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THE SALIVARY FACTOR AND ITS RELATION TO DENTAL CARIES AND IMMUNITY IN DEMENTIA PRAECOX AND EPILEPSY

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In a previous paper (1) it has been shown that a definite relationship exists between the neutralizing power of the normal resting saliva and that of the activated saliva. This relation, called the salivary factor, has been found to be indicative of the incidence of susceptibility to dental caries and of immunity therefrom, but is independent of oral cleanliness or the lack of it. The factor, while *not* an infallible test, has suggested a theory of one of the causes underlying the conditions of acquired and of absolute immunity.

In bacteriological work we find that by altering the acidity or the alkalinity of a culture medium, the growth of the organism may be inhibited. The application of this principle to oral conditions is obvious. Assuming the correctness of the salivary factor it will be found that in the condition of dental caries, the relationship of the neutralizing power of the activated saliva to that of the normal resting saliva varies only between relatively narrow limits. With immunity, the conditions are exactly the reverse and the relationship varies within relatively wide limits. The lactic acid-forming organisms, although capable of growth in a relatively high alkaline medium, flourish *more readily* in one of lesser alkalinity, such as may be furnished by the saliva found associated with caries. With the increase of growth of these bacteria there is a corresponding increase in the amount of lactic acid formed and the consequent solution of the calcium salts of the tooth structure.

In the further consideration of the neutralizing power the question arose as to whether the salivary factor is as constant in certain types of nervous disorders as it is in the normal individual.

A series of analyses were made on exactly the same lines as formally the cases being: first dementia praecox; second, epilepsy.

Contrary to the expectations of several members of the medical staff of the different hospitals as well as to the writer, it was found that coöperation, in securing samples from dementia praecox patients, was better in the more acute types. Those, on the other hand, who were of a higher mentality failed in nearly every instance to give the necessary voluntary aid. The majority of cases reported are women for it was necessary to eliminate the undetermined influence of the tobacco stimulus, which has curtailed the work, to a certain extent, among the men. Only typical cases of caries and of immunity were chosen. The reports are in terms of cubic centimeters of two-hundredth normal solutions and are based on 10 cc. of saliva as sample.

In these tests, as well as in those previously reported, the *exact* H^+ ion concentration in the saliva is not the determination which is sought. What is measured is a quite different quantity and one which is probably much less subject to adventitious variation, namely, the *power of the saliva to maintain its H^+ ion concentration near to that of neutrality.* We determine, by means of arbitrarily chosen indicators, corresponding to arbitrarily chosen H^+ ion concentrations, on either side of absolute neutrality, the amount of reagent (acid or alkali) required to change the H^+ ion concentration of the saliva from the one arbitrarily selected value to the other. The greater this amount the greater is the power of the saliva to maintain an H^+ ion concentration which lies between these limits in the neighborhood of absolute neutrality. The quantity thus determined is, therefore, correctly to be regarded as a measure of the "*neutralizing power*" of the saliva. The salivary factor is the ratio of the neutralizing power of the normal resting saliva to that of the saliva activated by chewing paraffin, expressed in percentage.

In table 1 is given the results of analyses from those patients whose teeth were at the time free from caries and who were denoted as possessing present immunity. It will be observed that the salivary factor is below 80 per cent and therefore, indicative throughout of this condition. A peculiar fact, which has been brought out in this series of tests, is, that in over 42 per cent of the cases, the activated saliva was *alkaline*, instead of acid, to phenolphthalein. In the reporting of these

TABLE 1

Dementia praecox

	NORMAL RESTING SALIVA			ACTIVATED SALIVA			
No. of patient	Neutrality to P-nitro-phenol = cc. N/200 HCl	Neutrality to phenolphthalein = cc. N/200 NaOH	Neutralizing power	Neutrality to P-nitro-phenol = cc. N/200 HCl	Neutrality to phenolphthalein = cc. N/200 NaOH	Neutralizing power	Salivary factor
Present immunity without care							
B- 5	12.60	4.80	17.40	37.05	−2.00 alk.	35.05	49.64
B-13	36.80	14.40	51.20	No coöp	eration		
B-14	8.00	31.60	39.60	No coöp	eration		
B-21	13.70	4.60	18.30	31.40	−3.50 alk.	27.90	65.59
Present immunity with care							
B- 3	12.10	9.30	22.40	37.30	4.00	41.30	54.24
B-22	9.50	5.50	15.00	26.90	0.95	27.85	53.86
B-23	18.55	1.90	20.45	32.00	−4.75 alk.	27.25	75.10
B-25	17.55	5.30	22.85	48.20	−3.60 alk.	44.60	51.23

analyses, the alkalinity, as indicated by a minus sign, has been deducted, for the determination of the neutralizing power, from the alkalinity as found with para-nitro-phenol. This alkalinity to phenolphthalein appears to be irrespective of oral conditions as it was found in both caries and immunity.

In table 2, the tabulations are compiled from analyses of the saliva found associated with dental caries. According to the reports previously made upon the normal individual, the salivary factor should be above 80 per cent. These findings are again confirmed in the following figures. It will likewise again be noted that there is a marked lack of uniformity in the acidity determinations, but in spite of this irregularity, however, the salivary factor remains remarkably constant.

In the case of a cretin, patient B-26, two separate analyses are given. The variation of a little over 5 per cent may be considered as within the limits of the experimental error; for the neutralizing power of both normal resting saliva and activated saliva checks to within 2 per cent. This patient was a man sixty years old and an inmate since 1881. The bony development in this particular case is noteworthy. The zygoma, mandible, and mastoid process are sensitive to pressure. About an

TABLE 2

Dementia praecox

No. of patient	Normal resting saliva: Neutrality to P-nitro-phenol = cc. N/200 HCl	Normal resting saliva: Neutrality to phenolphthalein = cc. N/200 NaOH	Normal resting saliva: Neutralizing power	Activated saliva: Neutrality to P-nitro phenol = cc. N/200 HCl	Activated saliva: Neutralily to phenolphthalein = cc. N/200 NaOH	Activated saliva: Neutralizing power	Salivary factor
Carious without care							
B- 1	12.60	6.50	19.10	19.90	−3.40 alk.	16.50	115.8
B- 2	11.05	18.25	29.30	30.05	−5.20 alk.	24.85	117.91
B- 4	4.60	28.50	33.10	43.60	−2.50 alk.	41.10	80.00
B- 6	17.60	9.80	27.40	29.10	−3.10 alk.	26.00	105.65
B- 7	11.00	9.80	20.80	21.70	−2.60 alk.	19.10	108.90
B- 9	19.80	4.60	24.40	22.70	1.20	23.90	102.10
B-11	17.40	6.00	23.40	20.00	2.90	22.90	102.10
B-12	19.20	1.40	20.60	21.00	2.40	23.40	88.03
B-20	18.65	12.00	30.65	40.90	−3.90 alk.	37.00	82.84
B-26	25.40	6.20	31.60	34.80	1.40	36.20	87.29
B-26	24.20	6.30	30.50	35.80	1.70	37.50	81.33
Carious with care							
B-10	9.85	6.10	15.95	16.05	2.00	18.05	88.60

inch anteriorly from the angle of the mandible there is a peculiar hard growth outward which appears to be attached to the remainder of the mandible by cartilage. The rate of salivary flow is apparently normal.

The next series of tables are compiled from data obtained from epileptics. In these cases the degree of acidity of the *activated* saliva is especially significant. Patient C-30, table 3, shows, for example, an acidity of the *normal resting* saliva of 2.65 cc. $\frac{N}{200}$ NaOH and the activated sample, instead of being of a lesser degree of acidity has increased to 3.30 cc. This is contrary to other observations that the acidity of the activated saliva is less than that of the normal resting saliva. In fact there is a very evident lack of uniformity in the acidity determinations in the work on dementia praecox and epilepsy, as compared with like determinations made on samples from the normal individual.

In table 4 are data from patients which show a comparison between the analyses of saliva taken during an epileptic seizure, with those

TABLE 3

Epilepsy

No. of patient	Date of last recorded convulsion	Severity of convulsion	Time at which sample was secured	Normal resting saliva: Neutrality to P-nitro phenol = cc. N/200 HCl	Normal resting saliva: Neutrality to phenolphthalein = cc. N/200 NaOH	Normal resting saliva: Neutralizing power	Activated saliva: Neutrality to P-nitro phenol = cc. N/200 HCl	Activated saliva: Neutrality to phenolphthalein = cc. N/200 NaOH	Activated saliva: Neutralizing power	Activated saliva: Salivary factor
Immunity without care										
										per cent
C-30	July 9	severe	July 12	22.80	2.65	25.45	36.25	3.30	39.55	64.35
C-31	July 6	severe	July 12	22.55	1.40	23.95	44.25	1.45	45.70	52.41
C-36	July 6	severe	July 13	14.85	5.95	20.80	38.05	−2.60 alk.	35.45	58.67
C-39	July 6	severe	July 13	8.90	4.45	13.45	24.70	1.95	26.65	50.09
C-44	June 6	light	July 13	23.60	2.20	25.80	44.80	−5.55 alk.	39.25	65.73
C-47	May 15	light	July 14	27.25	1.10	28.35	53.25	−4.50 alk.	48.75	58.15
C-48	July 7	light	July 14	16.05	6.40	22.45	38.05	−1.40 alk.	36.65	61.24
C-49	July 5	light	July 14	17.90	5.90	23.80	52.25	1.75	54.00	44.07
C-52	July 12	light	July 14	23.65	2.00	25.65	25.30	5.30	30.60	83.81
C-54	July 7	severe	July 14	20.25	3.30	23.55	38.90	−3.80 alk.	35.10	67.10

TABLE 4

Epilepsy

NORMAL RESTING SALIVA							ACTIVATED SALIVA			
No. of patient	Date of last recorded convulsion	Severity of convulsion	Time at which sample was secured	Neutrality to P-nitro phenol = cc. N/200 HCl	Neutrality to phenolphthalein = cc. N/200 NaOH	Neutralizing power	Neutrality to P-nitro phenol = cc. N/200 HCl	Neutrality to phenolphthalein = cc. N/200 NaOH	Neutralizing power	Salivary factor
Carious with care										
										per cent
C-27	July 12		July 12	18.85	3.35	22.20	22.80	1.40	24.20	91.73
C-27	July 14	light	during convulsion				4.30	27.80	32.10	
C-32	July 9	severe	July 12	24.95	2.45	27.40	26.65	1.30	27.95	98.03
C-32	July 14	light	during convulsion				2.10	26.30	28.40	

taken during a quiet period. In the case of C-27 the *first* sample was taken five hours after a seizure and the *second*, two hours later *at the time of a seizure*. The acidity, in the first instance, of the activated saliva, is 1.40 cc. $\frac{N}{200}$ NaOH, and in the second has increased to 27.80 cc. In the case of patient C-32 the first sample was taken three days after a severe seizure. Two days later a *second sample was obtained during a convulsion*. In this instance also is noted a marked increase of acidity in the second sample. Coexistent with this increase there is a corresponding decrease in the alkalinity which tends to render constant, within the variation of the experimental error, the total neutralizing power of this activated sample.

In table 5 patients C-28, C-29, C-33, C-35, C-46, and C-53 all present the same characteristics as previously noted. Another interesting point brought out by these experiments is the fact that the saliva regained its "normality" in twenty to thirty minutes after all symptoms of the seizure subsided. Patient C-40, an example of this, is reported below. The patient wore artificial dentures and the clinical conditions, therefore, could not be determined.

The results of the analyses are as follows:

NORMAL RESTING SALIVA							ACTIVATED SALIVA			
No. of patient	Date last recorded convulsion	Severity of convulsion	Time at which sample was secured	Neutrality to P-nitro phenol = cc. N/200 HCl	Neutrality to phenolphthalein = cc. N/200 NaOH	Neutralizing power	Neutrality to P-nitro phenol = cc. N/200 HCl	Neutrality to phenolphthalein = cc. N/200 NaOH	Neutralizing power	Salivary factor
C-40	July 13, 10 a.m.	Very severe	July 13, 3.30 pm	19.35	6.70	26.05	22.70	2.65	25.35	102.75
C-40	July 13, 5.50 p.m	Very severe	July 13, 6.15 p.m	19.40	4.30	23.70	26.70	−3.50 alk.	23.20	102.1

The second sample was secured *twenty minutes after* the seizure subsided. In this case the amount of saliva secreted at the *time of the convulsion* was too scanty to obtain a sample. This patient, a woman thirty-seven years of age, single, has been an epileptic for the past four years. It will be noted that the salivary factor varies less than 1 per cent which may be considered an unusually exact check for in the majority of cases the most careful analytical work will generally admit of no closer agreement than 5 per cent. The relatively high alkalinity to phenolphthalein, of the activated sample in second test, as shown

TABLE 5

Epilepsy

NORMAL RESTING SALIVA							ACTIVATED SALIVA			
No. of patient	Date last recorded convulsion	Severity of convulsion	Time at which sample was secured	Neutrality to P-nitro phenol = cc. N/200 HCl	Neutrality to phenolphthalein = cc. N/200 NaOH	Neutralizing power	Neutrality to P-nitro phenol = cc. N/200 HCl	Neutrality to phenolphthalein = cc. N/200 NaOH	Neutralizing power	Salivary factor
Carious without care										
										per cent
C-28	July 9	light	July 12	25.95	8.70	34.65	43.40	− 2.00 alk.	41.40	83.70
C-28	July 13	light	during convulsion				3.25	35.10	38.35	
C-29	July 12	severe	2 hrs. after convulsion	23.15	3.15	26.30	22.55	2.50	25.05	105.00
C-29	July 12	severe	during convulsion				3.60	28.10	31.70	
C-33	July 12	severe	July 13	11.35	8.50	19.85	20.90	2.25	23.15	85.75
C-33	July 13	light	during convulsion				6.70	26.90	33.60	
C-34	July 12	severe	July 13	17.45	5.00	22.45	51.10	−3.70	47.40	46.36exc
C-35	June 12	light	July 13 9 a.m.	13.55	7.00	20.55	22.85	3.30	26.85	78.40
C-35	July 13	severe	during convulsion				1.60	27.00	28.60	
C-37	July 13	light	2 hrs. after convulsion	24.50	6.90	31.40	26.05	2.70	28.75	109.22

C-38	July 10	severe	July 13	24.25	5.00	29.25	26.60	−0.60 alk.	26.00	112.50
C-41	June 1	severe	July 13	16.25	17.75	34.00	19.15	2.80	21.95	154.90
C-43	July 10	light	July 13	44.00	−4.00 alk.	40.00	36.20	−2.50 alk.	33.70	118.69
C-45	July 13	severe	2 hrs. after convulsion	16.10	4.75	20.85	22.45	−3.50 alk.	18.95	110.02
C-46	July 14	severe	½ hrs. after convulsion	14.75	5.85	20.60	12.20	3.55	15.75	130.80
C-46	July 14	severe	during convulsion				2.40	27.60	30.00	
C-51	July 13	severe	July 14	17.60	14.05	31.65	25.25	3.35	28.50	111.05
C-53	July 10	severe	July 14	28.70	6.00	34.70	37.60	−1.50 alk.	36.10	96.12
C-53	July 15	severe	during convulsion				7.00	26.20	33.20	
C-50	July 13	severe	July 15	27.15	2.55	29.70	34.25	1.35	35.60	83.43

by the minus sign, does not markedly alter the relationship of the normal resting saliva to the activated saliva, for the neutralizing power, as determined separately has been maintained constant to within a relatively small variation.

Consider these data from a physiological standpoint. The muscular convulsions incident with an epileptic seizure of the severe type, referred to by Osler (2), as the grand mal, in contradistinction to the petit mal, in which the convulsions are very much less marked, increase the formation, in the tissue, of the oxidative resultant, namely, the para-lactic acid. Halliburton (3) in discussing the chemistry of muscle during work says that "It (para-lactic or sarco-lactic acid) is the lactic acid par excellence of muscle. It is found also in the blood *especially after* muscular activity." Although some authors discuss at great length the probability of the proteid origin of lactic acid as for instance Bohm (4), Latham (5), Araki (6) and Hammersten (7) the consensus of opinion favors the glycogen theory. Both Halliburton (3) and Howell (8) assume that the stored glycogen of muscle is first converted to dextrose by the action of an amylolytic enzyme and then the dextrose is split according to following:

$$C_6H_{12}O_6 = 2C_3H_6O_3 \text{ and finally to } CO_2 \text{ and } H_2O$$

Since the genesis of the secretion of the salivary glands is in the blood (Halliburton) (9) it follows that the increased acidity of the saliva, produced during a seizure, is due to the corresponding increase of acidity in the blood resulting indirectly from the muscular work.

SUMMARY

1. That the neutralizing power of the saliva secreted by individuals suffering from dementia praecox bears a definite relationship to oral conditions.

2. That this relationship is the same as that observed in the normal individual.

3. That the neutralizing power of the saliva secreted by individuals suffering from epilepsy shows the same relationship to all conditions.

4. That during the time of muscular activity incident to an epileptic seizure the acidity of the saliva is markedly increased.

5. That the *alkalinity of saliva* produced during this period of stress is correspondingly lowered thus holding constant its total neutralizing power.

6. That the normality of the saliva is regained within thirty minutes after symptoms of the seizure have subsided.

BIBLIOGRAPHY

(1) Marshall: This journal, 1915, xxxvi, 260.
(2) Osler: Modern Medicine, vii, 655.
(3) Halliburton: Biological Chemistry of Muscle and Nerve. Philadelphia, 1904, 33.
(4) Bohm: Pflugers Arch., xxiii, 44; xlvi, 265.
(5) Latham: Brit. Med. Journ., 1886, i, 630.
(6) Araki: Zeitschr. of Physiol. Chem., 15-19.
(7) Hammersten and Hedirl: Textb. of Physiol. Chem., 7th ed., 583. (transl. by Mandel).
(8) Howell: Textbook of Physiology, 4th ed. Philadelphia, 1912, 66.
(9) Halliburton: Handbook of Physiology, 12th ed., 1915, 500.

THE EFFECTS OF THE SUBCUTANEOUS INJECTION OF ORGAN EXTRACTS UPON THE FLOW OF PANCREATIC SECRETION

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In our last communication upon the physiology of organ extracts(1) we summarized the results of our previous experiments. We found that the non-coagulable, or residue, portion of the aqueous extract of certain organs seemed to contain all of the material which showed demonstrable physiological activity. The residues of the pituitary, pineal, thyroid, parathyroid, thymus and adrenal glands, and of the liver, spleen and pancreas seemed each to exert a characteristic effect upon the blood pressure, respiration and heart action (2) and upon the contraction of unstriated muscle fibre (3). The action of the residues upon unstriated muscle fibre seemed to be exerted through the terminal filaments of the nerve supply of the muscles. The residue or non-coagulable portion of some of these extracts seemed also to have a more or less specific effect upon the gastric secretion, and the thyroid residue proved in addition to be a vigorous stimulant of gastric peristalsis (1).

The following communication deals with the effects of the coagulable and non-coagulable, or residue, portions of aqueous extracts of organs upon the flow of pancreatic secretion. Dogs were employed for the tests, and females were found, as a rule, to be more easily handled than males.

The lower and larger pancreatic duct, or that of Wirsing, was cut out of the wall of the duodenum, together with a small portion of the surrounding gut, and sutured into a median laparotomy wound. After healing had ensued, the dog was placed in a frame, and the flow of pancreatic juice from the fistula was estimated by counting the drops during five minute periods. The normal average flow per minute was thus determined during fifteen minutes. No food was given to the

animal for twelve hours before the experiment and none immediately afterwards.

The test material was standardized according to its nitrogen content, and equal amounts were injected aseptically into the subcutaneous tissue of the back or loin.

After having determined the normal flow, the injection of the test material was made and the drops from the fistula during many succeeding five minute periods were counted and recorded as in the table. Some ten or a dozen animals were employed and the table which give the record of an individual animal is typical of the results obtained.

In the course of these experiments it was apparent that external conditions or impulses, which presumably originating in the central nervous system, had a considerable influence upon the rate of flow from the fistula. Any excitement of the animal seemed to check the discharge immediately. This factor made the experiments somewhat unsatisfactory, but the results appeared to be of sufficient interest to warrant their publication. It is well recognized that an increase of the gastric secretion, and especial, of its hydrochloric acid, stimulates the flow of pancreatic secretion. In our last communication in this series (1) we demonstrated that the residues or non-coagulable portions of an aqueous extract of the thyroid and parathyroid glands and of the liver, pancreas and spleen increased both the amount and the acidity of the gastric secretion. In the following table it will be noted that the residue of the parathyroid gland and of the spleen and pancreas, although they stimulate gastric secretion, do not stimulate that of the pancreas. The thymus residue did not appreciably increase flow of gastric secretion, but was a most vigorous stimulant of the flow from the pancreas. The liver residue proved to be a most active stimulant for both the gastric and pancreatic secretion. But it stimulates the pancreas so soon after the injection that the effect seems the result of a direct action rather than through the increase of a secretion of hydrochloric acid.

The delayed stimulant effect of the thyroid residue suggests that it may be indirect, and secondary to the gastric mechanism. On the other hand the similar delayed effect of the thymus residue which does not appreciably increase the gastric secretion suggests that the thymus residue may act directly upon the pancreas. The adrenal residue inhibits the flow of the pancreatic secretion. The effects of the adrenal residue are approximately the same as those of the usual 1:1000 solution of adrenalin chloride.

		DROPS IN 1ST 5 MINS.	DROPS IN 2ND 5 MINS.	DROPS IN 3RD 5 MINS.	DROPS IN 4TH 5 MINS.	DROPS IN 5TH 5 MINS.	DROPS IN 6TH 5 MINS.	DROPS IN 7TH 5 MINS.	DROPS IN 8TH 5 MINS.	DROPS IN 9TH 5 MINS.	DROPS IN 10TH 5 MINS.	DROPS IN 11TH 5 MINS.	DROPS IN 12TH 5 MINS.	DROPS IN 13TH 5 MINS.	DROPS IN 14TH 5 MINS.	DROPS IN 15TH 5 MINS.	DROPS IN 16TH 5 MINS.	DROPS IN 17TH 5 MINS.	DROPS IN 18TH 5 MINS.	DROPS IN 19TH 5 MINS.	DROPS IN 20TH 5 MINS.	AVERAGE PER MIN.
Thyroid residue	Normal	5	5																			1.0
	After injection		4	3	3	2	2	1	4	3	6	17	35	37	36	38	37	38	34	29	30	3.8
Thyroid coagulable	Normal	8	7	7																		1.5
	After injection	1	14	13	12	9	12	15	27	11	11	8	0	4								2.1
Liver residue	Normal	6	11	12																		2.7
	After injection		15	17	25	27	32	37	48	52	56	59	47	55	54	47	64	52				7.1
Liver coagulables	Normal	11	9	13																		2.2
	After injection		16	25	11	9	11	5	7	3	7											2.1
Thymus residue	Normal	11	17	10																		2.5
	After injection	8	8	7	8	11	11	27	31	31	39	48	49	49	34	33	38	43	39	41		5.9
Thymus coagulables	Normal	21	19	20																		4.0
	After injection	17	16	14	13	10	12	13	12	12	11	7										2.5
Adrenal residue	Normal	10	10	10	6																	1.8
	After injection	3	24	14	5	2	2	2	1	2	2	1	1	1								0.9
Pancreas residue	Normal	22	16	15	13	13	21	17	14													3.5
	After injection	10	15	16	17	12	12	7	7	8	9	7	5	4								2.0
Spleen residue	Normal	13	15	14																		2.8
	After injection	10	9	4	3	13	17	22	20	5	4											2.3
Pituitary residue	Normal	26	21	23																		4.6
	After injection	7	6	15	13	15	22	16	18	16	19	20										3.0
Parathyroid residue	Normal	15	25	12	11	11																3.0
	After injection	12	10	9	7	6	19	13	3	13	9	12										2 1
Adrenalin	Normal	26	24																			5.0
	After injection	30	10	3	1	2	3	1	3													1.3
Effects of feeding	Normal	11	10	10																		2.0
	Three hours later	44	34	26	34																	6.9

All of these results agree with those previously obtained in localizing the active principles of any organ in the non-coagulable or residue fraction portion of its aqueous extract.

CONCLUSIONS

1. The effect of the subcutaneous injection in dogs of the residue, or non-coagulable portion, of an aqueous extract of the liver is the immediate and vigorous stimulation of the external secretion of the pancreas.

2. The residues of the thyroid and thymus produce a somewhat less vigorous and later response.

3. The residues of the pituitary and parathyroid glands and of the spleen and pancreas are inert.

4. The residue of the adrenal gland, like adrenalin, vigorously inhibits the intestinal secretion of the pancreas.

5. Only the residue or non-coagulable portion of an aqueous extract of the above mentioned organs shows any appreciable effect upon the intestinal secretion of the pancreas.

6. From these, and from the tests previously reported, we conclude that the residue or non-coagulable portion of an aqueous extract of the pituitary, pineal, parathyroid, thymus and adrenal glands and of the liver, spleen and pancreas contains practically all of the material from each of these organs which can directly and immediately affect through the circulation the functional activity of any other organ.

BIBLIOGRAPHY

(1) Rogers, Rahe, Fawcett, Hackett: This journal, 1916, xxxix, 345.
(2) Fawcett, Rogers, Rahe: This journal, 1915, xxxvii, 453.
(3) Fawcett, Rahe, Hackett, Rogers: This journal, 1915, xxxix, 154.

ACCELERATION OF GROWTH AFTER RETARDATION[1]

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In studying the curves of growth of a considerable number of albino rats in which, for a diversity of reasons, growth had been inhibited for varying periods, we have been impressed by the unexpectedly accelerated rate at which the increment of body weight may be resumed when the conditions are favorable. The circumstances preceding the renewal of growth in these instances were not directly comparable with those determining the rapid increase in weight that follows considerable depletion of the body substance. We have already published illustrative charts showing "curves of repair" after a considerable decline in body weight due to feeding with a defective diet (1). They indicate that under suitable dietary conditions lost weight may be regained far more rapidly than during normal growth through the same range of body weight. It was pointed out in our earlier publication that the chemical or metabolic processes of repair are probably by no means identical with growth. They may not involve the destruction and resynthesis of an entire protein molecule or of the entire protoplasmic cell structure. It is, furthermore, a familiar fact that repair or recuperation can take place at all ages, even after the completion of ordinary growth in the individual. The series of observations at present under consideration concern the weight changes subsequent to a more or less prolonged interruption of growth without any significant decline in body weight.[2]

[1] The expense of this investigation were shared by the Connecticut Agricultural Experiment Station and the Carnegie Institution of Washington, D. C.

[2] Rat 2523♂ forms an exception in that it had declined 78 grams from a body weight of 263 grams at a period considerably before the resumption of growth. The first rapid increase in weight in this animal thus in part includes a period of "repair."

It has been shown that the capacity to grow can be retained and exercised at periods far beyond the age at which growth ordinarily ceases (2). There seems to be no necessary impairment of the individual with respect to the ability subsequently to reach the full size characteristic of the species. Already in an earlier paper (2) it was noted that the rate at which growth is resumed after these prolonged delays need not be slow, and frequently actually exceeds the usual progress.

Anomalies of growth expressed by an exaggerated rate of growth are among the rarities of physiology. In referring to instances in the pathology of infancy Schloss writes:

> Was von excessiver Massenzunahme dem Kliniker häufiger vor Augen kommt, sind die Fälle, bei denen nach vorausgegangenem längeren Gewichtsstillstand, sei es durch Inanition, sei es durch Störungen der Entwicklung infolge von äusseren Schädigungen, das versäumte Wachstum schnell nachgeholt wird. Aber hier ist es fraglich, ob es sich um wirkliches Neuwachstum, also um eine enorme Beschleunigung der Zellteilung und Massenablagerung handelt; wahrscheinlich ist während des vorausgegangenen Entwicklungsstillstandes ein grosser Teil der Wachstumsarbeit schon getan, so dass nur noch die stoffliche Ausfüllung des Vorgebildeten übrig bliebe. In dem letzteren wahrscheinlicheren Fall gehörte diese Art 'Nachwachstum' zu den progressiven Korrelationsstörungen (3).

In other words whenever the growth of an entire organism as well as that of individual organs is modified in the sense of acceleration, this usually involves the reversal or return of a morbid condition to the normal. Further indications of the wide-spread uncertainty regarding the effects of retardations of growth have been expressed by Rubner, as follows: "We really do not know whether nature demands an absolutely uniform daily growth or whether remissions are permissible or perhaps even advantageous (4)."

In the case of children Boas (5) has reported that retarded individuals possess a late acceleration of growth. His statistical analyses show "that individuals whose prepubertal accelerated growth begins late in life have rates of growth that exceed by far those of the normal individual; in other words, that among the retarded individuals the whole energy required for growth is expended in a very brief period." Boas adds: "It seems very likely that the abnormally large amount of energy expended upon rapid growth during a short period is an unfavorable element in the individual development."

Schapiro (6) has found that if young kittens were chloroformed twice a day their growth was retarded in comparison with normal control

animals. However, on stoppage of the chloroform treatment, the greater rapidity of growth during an after period fully compensated for the earlier delay in development.

Quite recently Stewart (7) has reported the results of refeeding upon the growth of the body and of various organs of young albino rats after inanition for various periods. The growth in body weight of the rats refed after maintenance for various periods averaged considerably higher for some time than the normal for (younger) controls of the same body weight. Thus the stunted rats on refeeding were able to overtake the full-fed controls before the end of the normal growth period.

The accompanying tabular summary presents statistics of the accelerated growth which we have observed in illustrative instances. The "normal" figures for the average body weight at different ages and sexes in albino rats are taken for comparison from the most recent compilation of Dr. King (8) at the Wistar Institute. The retardation of growth was brought about in a variety of ways in the individual animals: sometimes intentionally, by the character of the diet fed; sometimes incidentally as the result of a failure on the part of the animals to eat enough of a supposedly adequate ration. Only those increments of size beyond the maximum weight previous to the resumption of growth are included in the figures recorded.

A few typical records are further illustrated in the appended graphic charts. These, as well as the summarized data, are practically self explanatory. An illustrative case may, however, be cited in detail to emphasize some of the points involved. Rat 2339 ♀ (see Chart I Appendix), for example, was maintained for some time without growth at a weight of about 100 grams until the late age of 402 days. At this age female rats (according to Dr. King's averages) weigh 220 grams. Growth was now resumed at an enormously exaggerated rate, so that *the rat put on 112 grams* and reached a weight of 216 grams *in 26 days*. The normal growth from 104 to 216 grams in female rats ordinarily requires 233 days. The record of Rat 2598 ♂ (see Chart II, Appendix) likewise may be cited, from among many others. It shows *a gain of 150 grams in body weight in 36 days* at a size which normally requires considerably more than two hundred days for the same growth accomplishment. These are merely typical cases. It will be observed that where the resumption begins early enough, these rapidly growing animals overtake the average growth record before growth is completed. There is also a tendency to reach a size decidedly larger than the average for this species.

Summary of changes in body weight in albino rats showing an accelerated rate of growth after retardation

RAT	AGE AT WHICH GROWTH WAS RESUMED	BODY WEIGHT WHEN GROWTH WAS RESUMED	AVERAGE NORMAL WEIGHT FOR THIS AGE	AVERAGE NORMAL SIZE REGAINED AT		TIME REQUIRED TO MAKE THE RECORDED GAIN IN BODY WEIGHT	
				Body weight	Age	In this experiment	In normal growth
♀	*days*	*gm.*	*gm.*	*gm.*	*days*	*days*	*days*
2446	426	198	216	218	438	**12**	86
2339[1, 6]	402	104	220	216	428	**26**	233
2369[1]	380	102	222	218	438	**58**	242
2476[1, 6]	322	116	221	220	400	**78**	244
1127[1, 3]	190	144	196	208	238	**48**	150
♂							
2523[2]	399	263	314	313	413	**14**	199
2552[2]	376	272	309	314	399	**23**	171
2520	352	225	304	310	394	**42**	258
2448[2]	350	290	304	304	354	**4**	56
2447[2]	348	236	303	309	371	**33**	238
2609	315	261	298	302	347	**32**	148
2611	312	249	298	301	363	**51**	171
2180[2, 6]	303	73	296	324	459	**156**	265
2549[2]	293	170	290	299	349	**56**	237
2598[2]	249	130	280	287	285	**36**	221
708[2, 5]	203	157	266	280	263	**60**	167
2293[2]	193	69	262	305	359	**166**	320
2911[2]	188	170	243	267	206	**18**	123
1568	157	117	248	280	257	**100**	185
2030	152	183	245	256	176	**24**	87
1204[3, 4]	145	129	241	272	224	**79**	161
1180[2]	136	133	234	272	223	**87**	158
1276[4]	112	133	211	260	188	**76**	123
1236	111	104	210	265	202	**91**	149
1076	83	90	170	253	168	**85**	121

[1] See Chart I, Appendix.
[2] See Chart II, Appendix.
[3] See Chart VI, Jour. Biol. Chem., 1913, xv, 325.
[4] See Chart I, Ibid., xvi, 433.
[5] See Chart I, Ibid., 1914, xviii, 104.
[6] See figure 5, Ibid., 1915, xxiii, 454.

Although these curves of "resumed growth" are usually far more "steep" than the normal curve of growth appears at any stage of its progress, the actual *percentage* increment is nowhere as large as is found in the earliest period of normal growth (9). Nevertheless the power of growth measured by the percentage rather than absolute increments of weight is decidedly greater than is ordinarily noted at the same

size in uninterrupted growth. The daily increments during "resumed growth" after the age of 100 days may equal 4 per cent, whereas normally they rarely exceed 1 per cent.

The ability of the individual to make exceptionally rapid gains of weight after a period of enforced maintenance without growth raises questions of broader biological interest. What has time accomplished in the interval of unchanged total body weight? Have developmental changes or cellular rearrangements proceeded? Have some of the cells (perhaps those of certain endocrine glands) advanced in their development more nearly normally than the great mass of the tissues? If so, they might exert an undue stimulus upon the energy transformations leading to growth. Stewart (7) has pointed out that there are variations in the relative weights of different viscera during maintenance without growth. The weight of some (including the hypophysis, testes and suprarenals) is even said to increase under such conditions. The explanation of the recorded phenomena of an exaggerated rate of growth after suppression of growth calls for elaborate histological studies of the important tissues during these periods of exceptional change.

SUMMARY

Records are presented to show that *after periods of suppression of growth*, even without loss of body weight, *growth may proceed at an exaggerated rate* for a considerable period. This is regarded as something apart from the rapid gains of weight in the repair or recuperation of tissue actually lost. Despite failure to grow for some time the average normal size may thus be regained before the usual period of growth is ended.

REFERENCES

(1) Osborne, T. B., and Mendel, L. B.: Journ. Biol. Chem., 1914, xviii, 95. (See Chart I.)

(2) Osborne and Mendel: Journ. Biol. Chem., 1915, xxiii, 439.

(3) Schloss, E.: Die Path. d. Wachstums im Säuglingsalter. Berlin, 1911, p. 35.

(4) Rubner, M.: Das Problem der Lebensdauer und seine Beziehung zu Wachstum und Ernährung. München und Berlin, 1908, 82; also Arch. f. Hygiene, 1908, lxvi, 82.

(5) Boas, F.: Science, 1912, xxxvi, 815.

(6) Schapiro, A.: Proc. Physiol. Soc., Journ. Physiol., 1905-06, xxxiii, p. xxxi.

(7) Stewart, C. A.: Proc. Amer. Assoc. Anat., New Haven Meeting, Dec., 1915, p. 75.

(8) King, Helen D.: Anat. Record, 1915, ix, 758; also in Donaldson, H. H., The Rat. Data and Reference Tables. Philadelphia, 1915, p. 69.

(9) Cf. Ferry, Edna L.: Anat. Record, 1913, vii, 433.

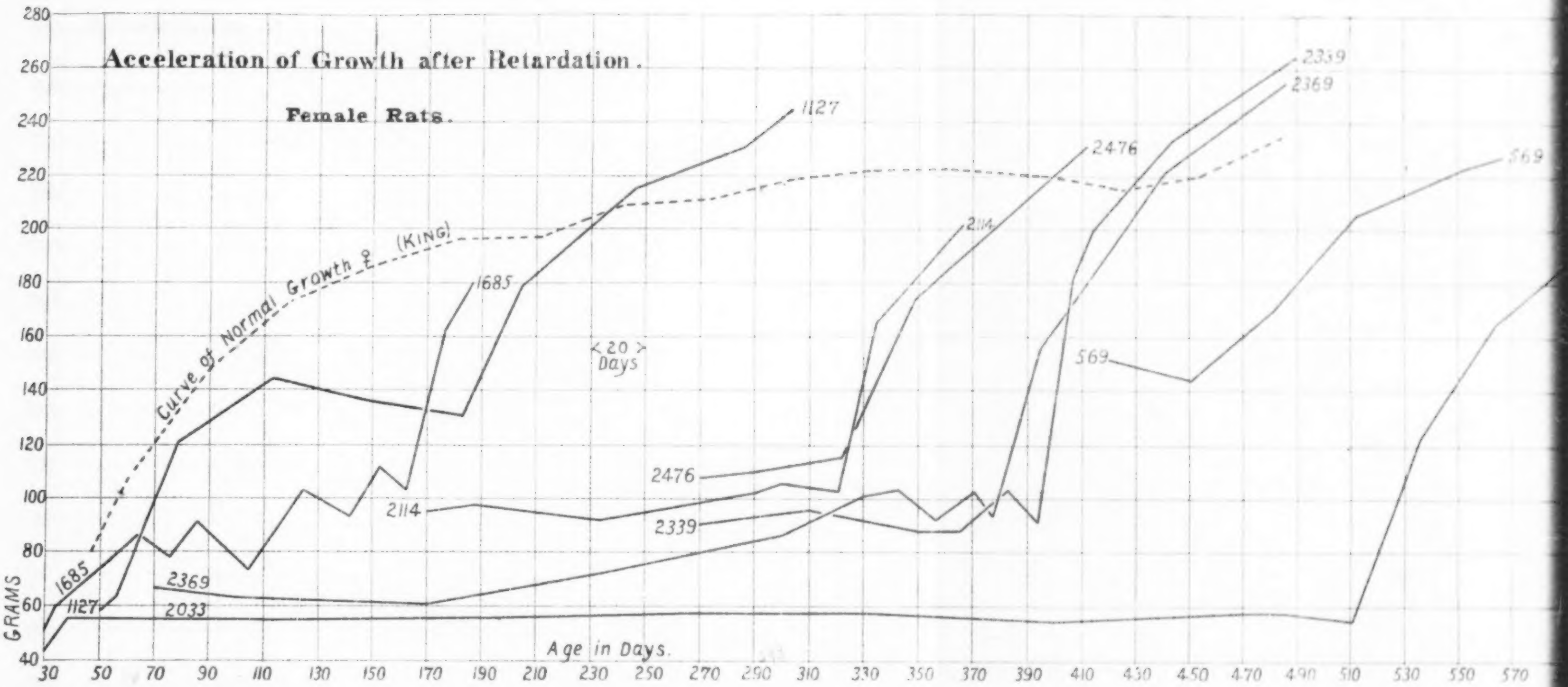
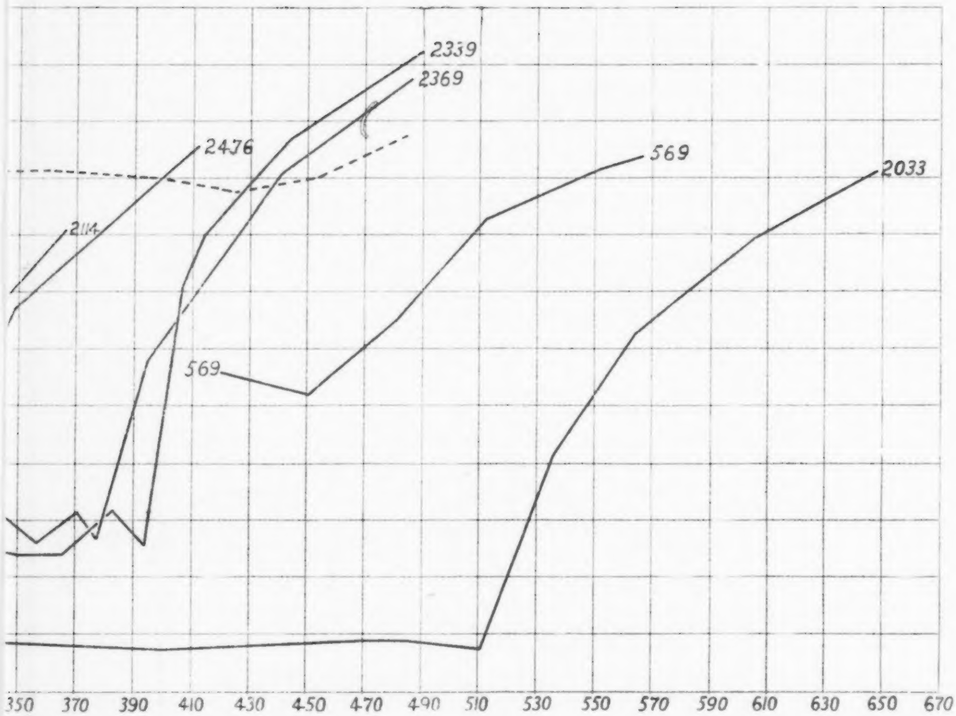


CHART I. Chart showing the increments of body weight in female albino rats after periods of varying length during which growth was retarded or completely
resumed in these animals at an accelerated rate far beyond that ordinarily observed for animals of comparable size under normal conditions of uninterrupted growt
these animals will be found in the tabular summary in the text.



of varying length during which growth was retarded or completely suppressed. Growth was
ls of comparable size under normal conditions of uninterrupted growth. Statistics for some of

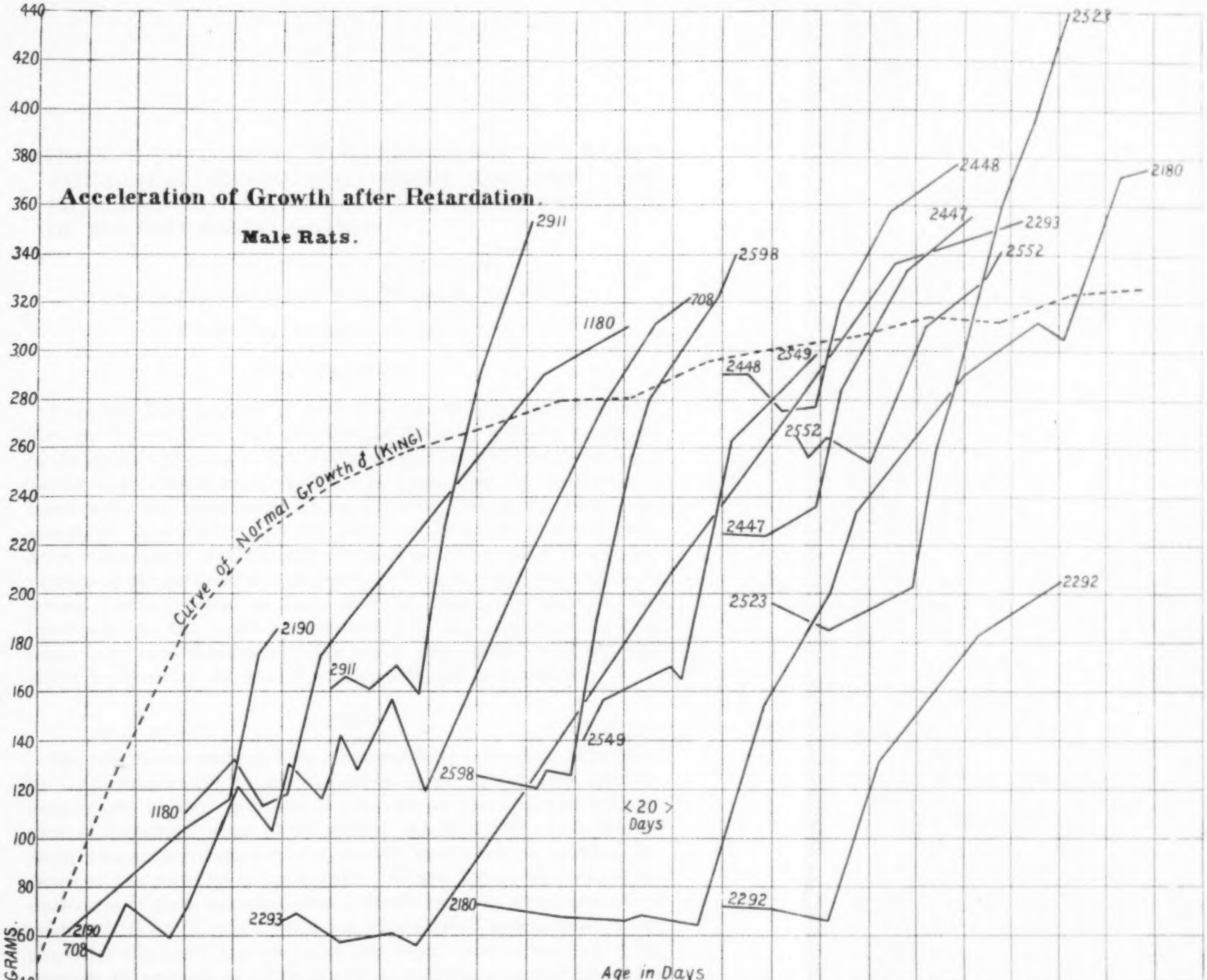


CHART II. Chart showing the increments of body weight in male albino rats after periods of varying length during which growth was retarded or completely suppressed. Growth was resumed in these animals at an accelerated rate far beyond that ordinarily observed for animals of comparable size under normal conditions of uninterrupted growth. Statistics for some of these animals will be found in the tabular summary in the text.

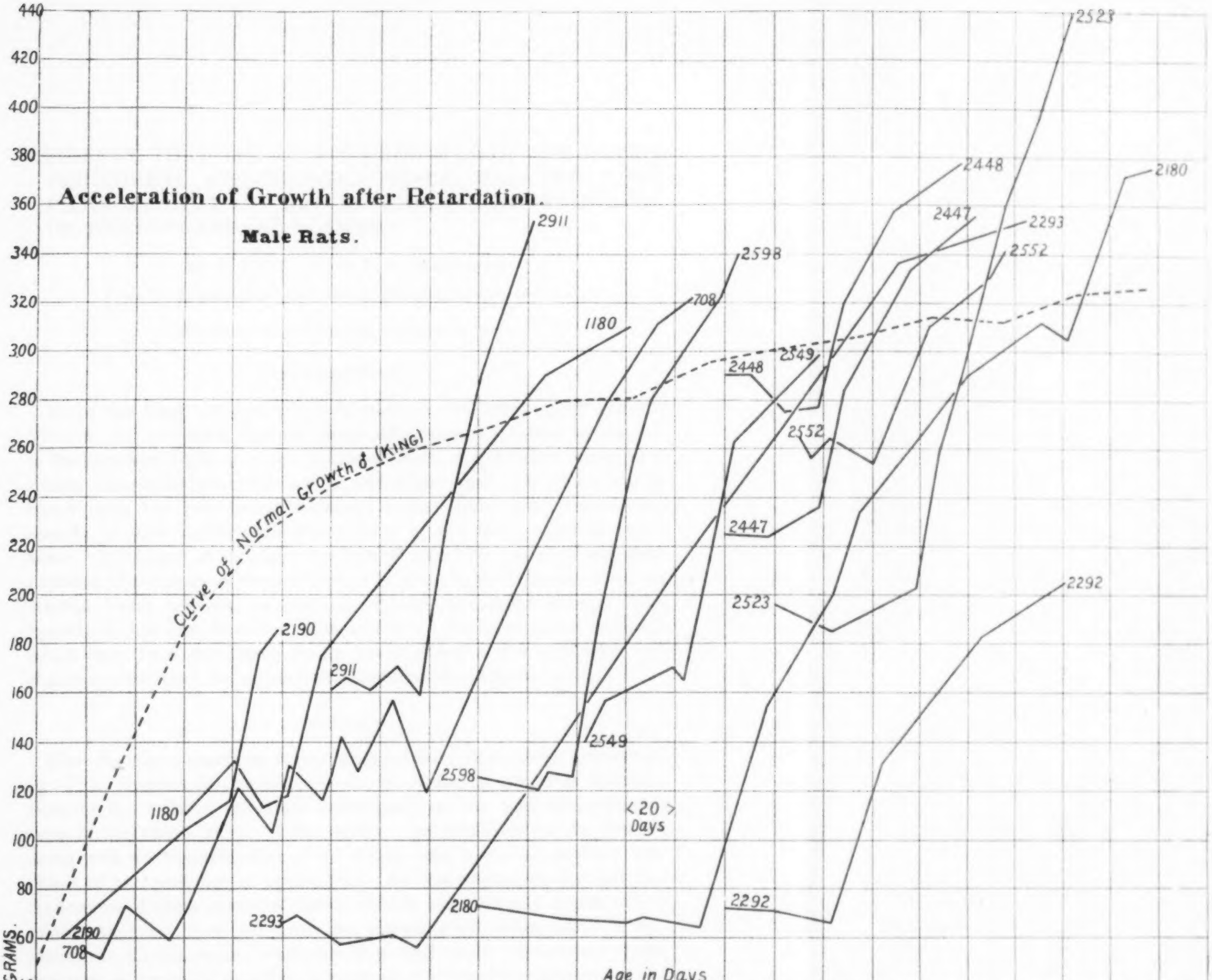
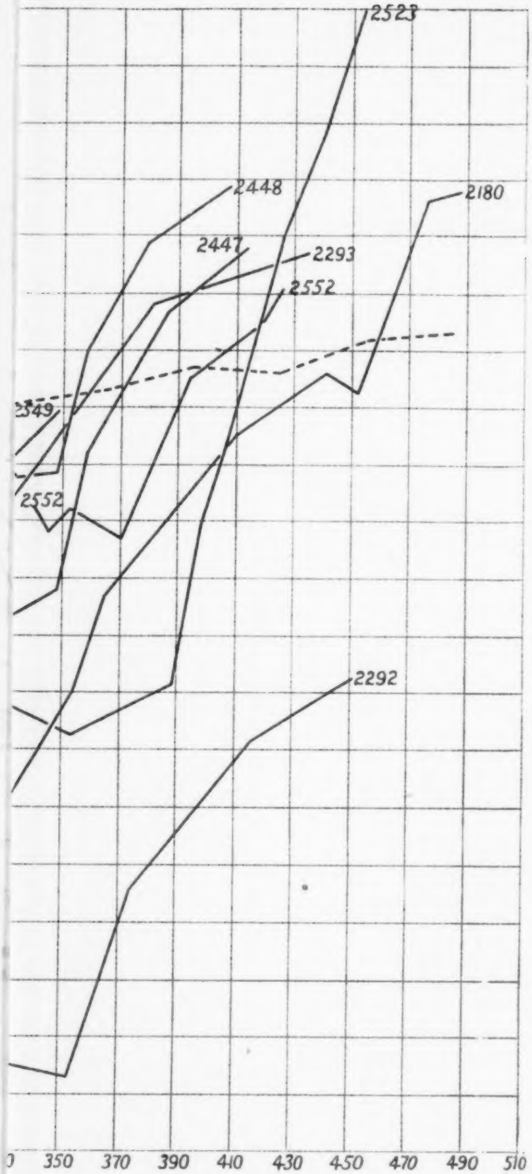


CHART II. Chart showing the increments of body weight in male albino rats after periods of varying length during which growth was retarded or completely suppressed. Growth was resumed in these animals at an accelerated rate far beyond that ordinarily observed for animals of comparable size under normal conditions of uninterrupted growth. Statistics for some of these animals will be found in the tabular summary in the text.



of varying length during which growth was retarded far beyond that ordinarily observed for animals of ıese animals will be found in the tabular summary in

EVIDENCE THAT THE ACTIVE PRINCIPLE OF THE RETRO-PERITONEAL CHROMAPHIL TISSUE HAS THE SAME PHYSIOLOGICAL ACTION AS THE ACTIVE PRINCIPLE OF THE SUPRARENAL GLANDS

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INTRODUCTION

From the large amount of work done on the chromaphil system, Vincent (1) concludes that all chromaphil tissue, whether contained in the suprarenal gland or not, yields adrenin, or a substance having a similar pharmacodynamical action, and states that this conclusion is based upon the provisional assumption that chromaphil tissues are specific in their nature, and everywhere of the same essential character. In support of this hypothesis Biedl and Weisel have shown that extracts of the retro-peritoneal tissues in man have the same effect on arterial blood pressure as extracts of the suprarenal glands. The hypothesis has not, however, been tested by the more exact methods which have been developed during recent years, and it was with this object in view that the present investigation was undertaken.

METHODS

The pharmacodynamical tests employed have been those advocated by G. N. Stewart (2), namely, the action on the spontaneous contractions of the isolated intestinal muscle and on the tone and contractions of the virgin uterus of the rabbit. An inhibition of the former, along with an augmentation of the latter, was taken as positive evidence of the presence of epinephrin. As was shown by Stewart, the occurrence of these opposite effects entirely removes any doubt which might otherwise be raised when one physiological action alone is employed; it eliminates any confusion that might arise on account of the presence of proteins or other pressor or depressor substances in the extracts.

Two similar muscle chambers of glass, one with a capacity of 50 cc., the other of 30 cc., were used for the intestinal and uterine preparations respectively. The lower end of the muscle chambers extended downwards through the vessel used as a waterbath. Two small capillary glass tubes were fastened in the lower end of each of the muscle chambers. One of the tubes was connected by rubber tubing to the oxygen tank. Through this tube very small bubbles of oxygen were allowed to escape into the solution. The other tube served as an outlet for withdrawing the solution contained in the chamber. In this way it was possible to change the fluids in the chambers with very little mechanical interference with the action of the muscle preparations. The preparations of intestine and uterus were quickly removed from the same (non-pregnant) rabbit.

The difficulty of detecting epinephrin in extracts of the retro-peritoneal chromaphil tissue is greatly enhanced by the fact that the protein of these extracts exerts a marked influence on the movements of the intestine and uterus. Protein causes a great increase in the tone of both muscle preparations. In the case of the intestine the epinephrin inhibition must overcome the pressor effects of the proteins present before it can manifest itself. In the case of the uterus, epinephrin causes an augmentation and acceleration of the uterine muscle; so also does protein.

In obtaining the retro-peritoneal chromaphil tissue for the physiological test, an attempt was made to get as much of the tissue as possible. The suprarenal glands were first carefully dissected out. The kidneys were next excised and discarded, care being taken to cut the blood vessels as near the organ as possible, as the chromaphil tissue is regularly found in the renal plexus. A small piece of tissue about a centimeter in length was next removed to serve as a histological check. The remainder of the abdominal aorta and surrounding tissues was carefully dissected out. The suprarenal glands and this retro-peritoneal tissue, with the exception of the above histological check, were, upon excision, washed free from blood and placed in the extracting solution.

In the earlier attempts the extracting solution consisted of Ringer's solution, but it was soon found that the larger percentage of protein and the rapid oxidation of epinephrin rendered the results very uncertain.

The method that was found to eliminate the source of error most satisfactorily was a modification of that which Folin, Cannon and

Denis (3) employed for the chemical assaying of the epinephrin in the suprarenal glands. The suprarenal glands and the retro-peritoneal tissues were put into separate beakers containing 10 cc. of a $\frac{N}{10}$ HCl solution plus a few cubic centimeters of distilled water. The tissue was then finely minced and macerated with sand in a mortar, after which the extract was transferred to a beaker with the addition of a few cubic centimeters of water and slowly brought to boiling. The extract was then expressed through surgical gauze to separate the sand and larger parts of tissue from it. The precipitate was again extracted with 5 cc. of $\frac{N}{10}$ HCl and a few cubic centimeters of distilled water. The filtrates were then poured together and the total volume of extract brought to 40 cc. by the addition of more distilled water. The total extract was again brought to boiling, when 5 cc. of a 10 per cent solution of sodium acetate was added and the boiling continued for a few minutes, after which the material was filtered. The extract of each tissue was then transferred to stoppered flasks in the waterbath until ready for use. The best results were obtained by neutralizing the extract (towards litmus) with a 10 per cent solution of sodium carbonate before applying it to the muscle preparation.

RESULTS

For convenience the results are presented in tabular form (table 1) a few of the curves from typical experiments being also given in figures 1, 2 and 3. It will be unnecessary here to do more than refer to the experiments in which the technique was modified, or the results obtained were out of the usual run, or refer to tissue in which some doubt has hitherto existed as to the presence of chromaphil tissue.

Regarding the mode of preparation and the optimum reaction of the extract, it was found that in extracts prepared by means of Ringer's solution from the tissues of a dog, those of the suprarenal glands caused inhibition of the movements of the intestinal muscle and augmentation and acceleration of the movements of the uterine muscle, whereas similar extracts of the retro-peritoneal chromaphil tissue gave an augmentation followed by a slight diminution of the movements of the intestinal muscle and an augmentation followed by a diminution of the uterine muscle, both reactions being probably due to protein, since similar extracts of the thoracic aorta and muscle tissues gave corresponding results. It was concluded that the epinephrin had oxidized during the process of extraction to such an extent that the inhibitory

effect of the epinephrin could not overcome the pressor effect of the proteins present.

In all the other observations on the dog, the method of acid extraction was employed and, as shown in the table, distinct evidence of epinephrin

TABLE I

NO.	ANIMAL INVESTIGATED	TISSUE EMPLOYED	HISTOLOGICAL CHECK	ACTION ON INTESTINE	ACTION ON UTERUS
1	Dog*	Retro-peritoneal	+	−	−
		Suprarenals		+	+
2	Dog	Retro-peritoneal	+	+	+
		Suprarenals		+	+
		Thoracic aorta		−	−
		Muscle		−	−
		Muscle + epinephrin		+	+
3	Cat	Retro-peritoneal	+	+	+
		Suprarenals		+	+
		Thoracic aorta		−	−
4	Dog	Retro-peritoneal		+	+
		Suprarenals		+	+
		Muscle		−	−
5	Rabbit	Retro-peritoneal	+	+	+
		Suprarenals		+	+
6	Guinea pig	Retro-peritoneal	+	+	+
		Suprarenals		+	+
7	White rat	Retro-peritoneal	+	+	+
		Suprarenals		+	+
8	Dog	Retro-peritoneal		+	+
		Suprarenals		+	+
		Thoracic aorta		−	−
9	Cat	Retro-peritoneal	+	+	+
		Suprarenals		+	+
10	Calf	Retro-peritoneal		+	+
		Suprarenals		+	+
11	Pig	Retro-peritoneal		+	+
		Suprarenals		+	+
12	Sheep	Retro-peritoneal		+	+
		Suprarenals		+	+
13	Child	Retro-peritoneal		−	−
		Suprarenals		−	−
14	Man	Retro-peritoneal		+	+
		Suprarenals		+	+

*Extracts prepared by Ringer's solution.

+ Under "Action on intestine" and "Action on uterus" indicates positive evidence of epinephrin.

− Indicates no epinephrin reaction.

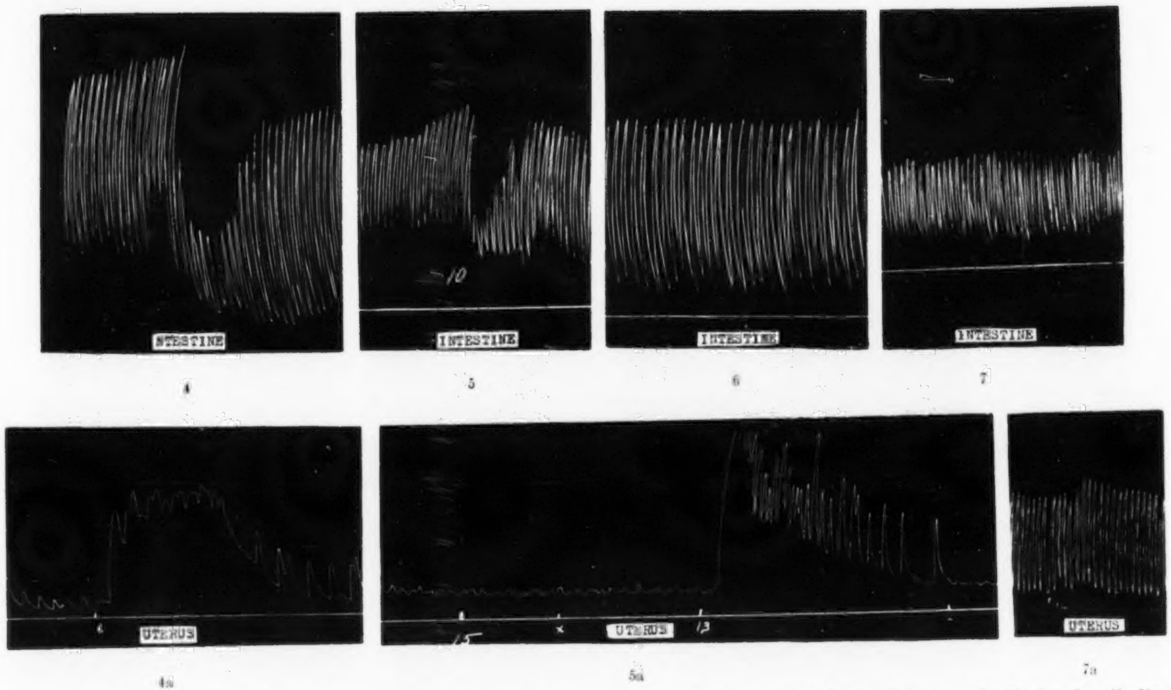

Fig. 1. Effect on intestinal and uterine contractions of: *4*, *4a*, extract of suprarenal gland of dog, made distinctly alkaline to litmus; *5*, *5a* (13), extract of retro-peritoneal tissue of dog, neutral to litmus; *6*, *5a* (15), extract of thoracic aorta; *7*, *7a*, extracting solutions alone.

was obtained in the retro-peritoneal tissue. In similar extracts prepared from other tissues, such as connective tissue, thoracic aorta, or muscle, no such results were obtained. Carefully prepared extracts of the sympathetic chain of ganglia and of the stellate ganglia, removed from several dogs, failed to give any indication of epinephrin. The result with the stellate ganglia is of interest, since chromaffin cells

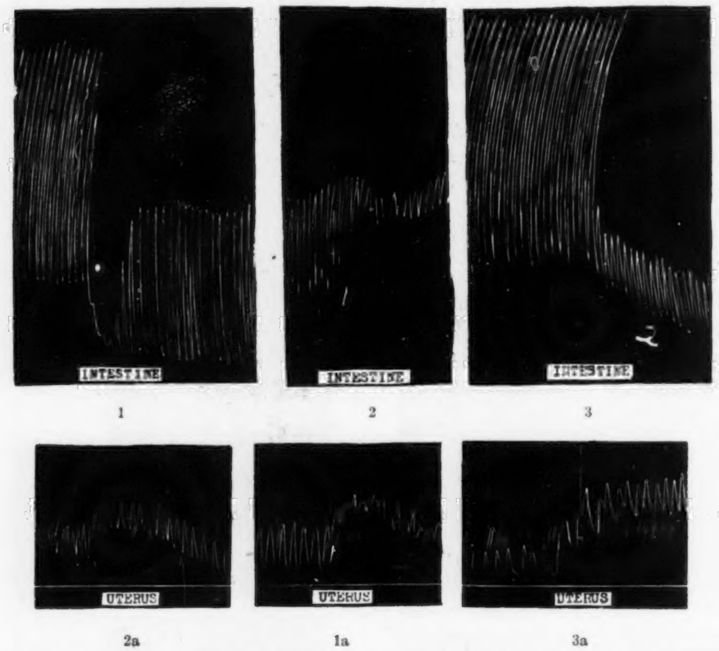

Fig. 2. To demonstrate the importance of using weak acid instead of Ringer's solution in preparing the extracts. *1*, *1a*, extract of suprarenal gland made by Ringer's solution; *2*, *2a*, extract of retro-peritoneal tissue of dog made by Ringer's solution; *3*, *3a*, extract of retro-peritoneal tissue of dog made by weak acid.

have been found present in them. Observations were made on the epididymis, in which such cells are also said to be present with negative physiological results. The most striking results were obtained when the solutions were as nearly neutral to litmus as possible (4). They were, however, left very slightly acid in order to prevent oxidation of the epinephrin.

Special interest attaches to the observations on the white rat, the guinea-pig and man. By the macroscopic method of Kohn, no chromaffin tissue can be demonstrated in the retro-peritoneal tissue of the white rat and guinea-pig, although one of us (M. E. F.) has found it in this position by the use of the histological method. Extracts of these tissues gave strongly positive reactions with the uterine and intestinal muscle (fig. 3) preparations, thus confirming the conclusion that retro-peritoneal chromaffin tissue is present in these animals.

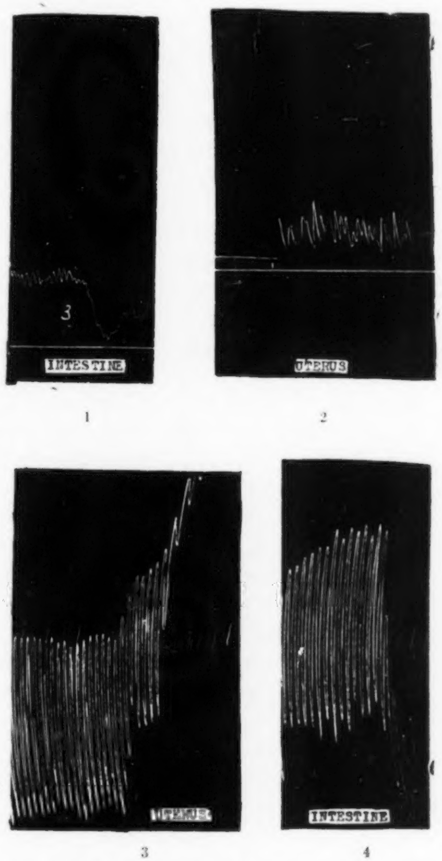

Fig. 3. To demonstrate effect of acid extract of retro-peritoneal tissue of white rat (*1* and *2*) and guinea pig (*3* and *4*) on intestine and uterus preparations.

The retro-peritoneal tissue obtained from a child three weeks old, which had died six hours after operative procedure for congenital hypertrophic stenosis of the pylorus, was after four days' time treated in the usual manner. The results obtained were negative, probably because of oxidation of the epinephrin in the tissues used. In the case of the retro-peritoneal tissue of a man, the results were positive. The subject used for this experiment was forty years old, mature, well-built and healthy. He was injured in an automobile accident and died of concussion of the brain four days after the injury. Five hours after his death, the retro-peritoneal tissue and suprarenal glands were excised and placed in the HCl solu-

tion. The tissues were immediately extracted and tested, and as stated above positive results were obtained.

In two instances where very dilute solutions of the retro-peritoneal tissue extract were added to the uterus, a purely inhibitory effect was observed; five times the same dose which gave this effect gave the usual augmentory result. Stewart (2) observed that this was true of epinephrin in very dilute solutions. In three instances when the extracts of retro-peritoneal tissue were added to the intestinal preparations, an augmentation and acceleration were noted. Increased doses of the same extract produced the usual effect. Whenever these opposite effects were noted, the muscle preparations were always immediately washed with Ringer's solution and allowed to return to normal, when increased doses were applied. These results are in conformity with those of Cannon, Stewart, Hoskins, etc., who observed that very dilute solutions of epinephrin produce augmentory effects on the intestinal muscle. Similar reversed effects of epinephrin had previously been noted by Moore and Purinton (5) in the action on the blood pressure, a fall instead of a rise being obtained when very small doses of epinephrin extracts were administered. Pari (6) found that in freshly prepared extracts there is never a lowering of blood pressure, but that with very dilute solutions which have been kept for some time, this may be observed. He suggests, therefore, that the depression is due to a chemical change in the epinephrin. The fact that we observed opposite effects for epinephrin on the muscle preparations when dilute solutions were added, and that the normal effects were observed after increased doses, shows that the above explanation cannot be accepted.

In some of the records made by the uterine muscle, it will be observed that the muscle was recording a straight line before the addition of the solution to be tested. It appears that a muscle which is quiescent and records a straight line, may be just as irritable to epinephrin as its companions which are recording small contractions. Usually, however, the active strips furnish the best test objects.

Histological checks were made on the dog, the cat, the rabbit, the white rat and the guinea-pig. The yellow staining bodies and cells were demonstrated in all of the checks taken from the retro-peritoneal tissue.

We are indebted to Prof. T. W. Todd for the sectioning and staining of the histological checks in connection with this work, and to Prof. H. T. Karsner for the human material.

CONCLUSION

Acid extracts of the retro-peritoneal chromaphil tissue of man, the dog, the cat, the rabbit, the guinea-pig, the white rat, the calf, the sheep, and the pig have the same physiological action on intestinal and uterine muscle as the active principle of the medulla of the suprarenal glands.

BIBLIOGRAPHY

(1) Vincent, Swale: Internal Secretions and the Ductless Glands. London, 1912.
(2) Stewart, G. N.: Journ. Exp. Med., 1912, xv, 564; ibid, xvi, 502.
(3) Folin, Cannon and Denis: Journ. Biol. Chem., 1912–1913, xiii, 477.
(4) Rona and Neukirch: Pflüger's Arch. f. die gesammt. Physiol., 1912, cxlviii, 273.
(5) Moore and Purinton: Pflüger's Arch. f. die gesammt. Physiol., 1900, lxxxi, 483.
(6) Pari, G. A.: Arch. ital. di Biol., 1906, xlvi, 209.
(7) Hoskins, R. G.: This Journal, 1912, xxix, 363.

THE REACTIONS OF STRIATED MUSCLE TO POTASSIUM CHLORIDE SOLUTIONS

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Since Overton pointed out that frog's striated muscle temporarily loses its irritability in solutions of potassium salts, and that these salts can be divided into two classes, according to the different effects which they have on muscle immersed in them (1), it has been shown by Siebeck (2) and by one of us (3) that Overton overlooked some important points regarding the reactions of muscle to potassium chloride. We agree with Overton in finding that frog's striated muscle maintains its original weight in isotonic solutions of dipotassium phosphate, and swells fairly rapidly in isotonic solutions of potassium chloride. But we disagree with him in regard to the permanently toxic effects of potassium chloride. It has been shown by Siebeck in the article referred to above that immersing a frog's sartorius in Ringer's solution may restore its original weight and irritability after it has been for four hours in 0.89 per cent potassium chloride solution at 0 to 4°C. In an experiment by one of us (Experiment 74 of the article cited above), a sartorius was kept for three hours in isotonic potassium chloride, and then for about twenty hours in Ringer's solution, the temperature throughout remaining near 16°. During the period in potassium chloride the muscle gained a little more than 30 per cent of its original weight and became, as was to have been expected, entirely unirritable. During the subsequent period in Ringer's solution, the muscle returned to a little less than its original weight and became as irritable as it was at the beginning. It is evident, therefore, that frog's sartorii may recover from the effects of an immersion in an isotonic potassium chloride solution.

The reactions of striated muscle to solutions of potassium salts are interesting from a number of different aspects, which need not be dwelt on here, and we have thought it advisable to try to gain some further light on the subject.

PRELIMINARY EXPERIMENTS

We began by trying experiments in which frog's sartorii were immersed for various periods in 0.9 per cent potassium chloride solutions at between 5 and 10°, and then transferred to Ringer's solution. Experiments 1, 2 and 3 are examples of these. They show that recovery from the potassium chloride effects may be quite complete after six hours' immersion; and that, even after a sartorius has been for twenty-four hours in the potassium chloride solution and increased in weight 100 per cent, it may still show some degree of recovery. It must be added, however, that the results of such experiments are very variable. In experiments similar to nos. 1, 2 and 3, but carried out later in the summer, we failed to get recovery after exposures to potassium chloride of much less than twenty-four hours. We are inclined to attribute these differences to changes undergone by the frog's tissues with the advance in the season.

ANALYSIS OF THE POTASSIUM CHLORIDE EFFECTS

The experiments to be reported under this heading may be regarded as a preliminary attempt to analyze the changes which go on in a frog's sartorius when it is immersed in a 0.9 per cent potassium chloride solution. It is obvious that the muscle takes up water, and very probable that it takes up potassium chloride. And these changes are probably accompanied by still others which are not quite so obvious, but still highly important for an understanding of the phenomena. In the following paragraphs the experiments bearing on the various changes, either known or suspected to occur, are reported seriatim.

Does muscle immersed in potassium chloride produce lactic acid? It is now well recognized that striated muscle produces considerable quantities of lactic acid when subjected to a great variety of abnormal conditions, and the question comes up whether or not immersion in potassium chloride solutions may have this effect. There are many reasons for thinking that this is the case. It is well known, for instance, that the chloride, as well as other salts of potassium, cause muscle to go into an abnormal form of contraction which is maintained for some minutes, and all the forms of contraction and rigor so far investigated have been shown to be accompanied by lactic acid production. The influence of temperature on the reactions of muscle to potassium chloride confirm the supposition under discussion. In order to show the recovery from the potassium chloride effects, Siebeck carried out his

experiments at between 0 and 4°. The experiments of one of us in the article referred to above show that the recovery from the potassium chloride effects is dependent on temperature. A muscle kept for six hours in 0.9 per cent potassium chloride solution at between 20 and 21° failed to recover its irritability, while another muscle kept for the same period in the same solution at between 2 and 8° did recover its irritability, very completely (4).

Another point, which indicates that the swelling undergone by muscle in a potassium chloride solution may be partly the result of lactic acid production by the muscle, is the interesting fact brought out by Siebeck, that sartorii swell faster in potassium chloride and recover less completely, if they be subjected to strong stimulation soon after their immersion (5). We have repeated this experiment and obtained similar results. We have found, however, as Siebeck implies, that in order to produce constant results the stimulation must be very strong—of such strength as would almost undoubtedly injure a normal sartorius. We found that more moderate stimulation[1] produced no constant effects either on the rate of swelling of muscle immersed in the potassium chloride solution, or on its subsequent tendency to recover its irritability.

The part played by lack of calcium in the potassium chloride effects. So far as we know, there is no solution of a single salt in which surviving muscle remains alive for any great length of time. A 0.6 per cent or 0.7 per cent sodium chloride solution is as little injurious as any other so far discovered, but in this solution an irritable muscle usually twitches continually, gains weight, and loses its irritability in less than twenty-four hours at ordinary room temperatures. Very small quantities of a soluble calcium salt added to the pure sodium chloride solution suffice to prevent the twitching and to greatly prolong the period during which the muscle remains irritable. It is possible, therefore, that the death of muscle in potassium chloride solutions may be due, in part, at least, to the absence of calcium, as well as to the direct effects of the potassium. We have tried experiments in which we have compared the results of

[1] As "moderate stimulation" we used a tetanizing current which could be borne without much discomfort on the tongue. Such a current would strongly stimulate a normal muscle, but would produce comparatively little injury; the individual shocks of which it is composed would be equivalent to from 400 to 1000 of Martin's Z units. As "strong stimulation" we used a current whose individual shocks would be equivalent to from 4000 to 8000 of Martin's Z units. See Martin: The Measurement of Induction Shocks; New York and London, 1912. We do not think it worth while to publish the protocols of these experiments.

immersing sartorii in pure 0.9 per cent potassium chloride solution with those of immersing them in mixtures of this with 1 per cent calcium chloride solutions.[2] The mixtures were made by adding 97.5 parts of the potassium solution to 2.5 parts of the calcium solution, and were, therefore, very nearly isotonic with the original potassium solution. It was found that the muscles gained weight more slowly in the potassium and calcium mixtures than in the pure potassium solutions, and that they recovered their irritability more completely when subsequently immersed in Ringer's solution. See Experiments 4 and 5.[3]

It is a tempting hypothesis that the calcium produces its effects by rendering the surfaces of the muscle fibers less permeable to the potassium chloride (6). This would explain the slower gain in weight in the potassium and calcium mixture, the more complete subsequent recovery, and also, to some extent, the fact that muscles which have been in the mixtures lose weight more slowly when subsequently immersed in Ringer's solution than do the muscles which have been in the pure potassium solutions. We thought that more light might be thrown on this question by immersing companion muscles in 0.9 per cent potassium chloride, and then transferring one to Ringer's solution and the other to pure 0.7 per cent sodium chloride solution and comparing the rapidity with which they lost weight. If it be supposed that the surfaces of the muscle fibers are permeable to potassium chloride, but still more or less impermeable to sodium chloride after their stay in the former solution, and that calcium renders them less permeable to the potassium chloride, the muscles ought to lose weight faster in the pure sodium chloride solution than in the Ringer solution which contains calcium. The results of these experiments are curious—the muscles show a tendency to maintain in the pure sodium chloride solution the weight which they happened to have when immersed in it. See Experiments 6, 7, 8 and 9. But the results are not sufficiently uniform to warrant any particular conclusion.

The diffusion of potassium chloride into sartorii immersed in 0.9 per cent solutions of it. It is a question of great interest to what extent the potassium chloride diffuses into muscle immersed in it, and how much chlorine is left after the recovery in Ringer's solution. We have analyzed

[2] A 1 per cent calcium chloride solution has about the same calculated osmotic pressure as a 0.9 per cent potassium chloride solution.

[3] Similar results were obtained in another pair of experiments, which we have not thought it necessary to publish.

muscle for chlorine after a stay of some hours in 0.9 per cent potassium chloride solution, and also after it has been for some hours in this solution and then recovered its irritability in Ringer's solution. See Experiments 10, 11, 12 and 13.

The results of Experiments 10 and 12 indicate that when muscle is immersed in 0.9 per cent potassium chloride solution, the salt rapidly diffuses into the fibers. In both experiments the proportion of chlorine found in the muscle after its stay in the solution was larger than could be accounted for by supposing that it takes up the solution as such. To use a somewhat crude expression, the potassium chloride diffuses into the muscle faster than the water of the solution.[4] If it be supposed that about half the original weight of the muscle consists of solids and organic water; and the other half of free water which can act as a solvent for salts (7), then it follows that at the end of Experiment 10 there was very nearly as high a concentration of potassium chloride in the total free water of the muscle as in the surrounding solution.

Experiments 11 and 13 give the chlorine content of muscles which have been for some time in 0.9 per cent potassium chloride solution, and have then recovered their irritability and returned to somewhere near their original weight in Ringer's solution. They are companions to Experiments 10 and 12. Their results show that, accompanying the loss of weight by the muscles in Ringer's solution, there is a considerable loss of chlorine. It seems difficult to interpret these results on any other supposition than that the muscle fibers, when placed in Ringer's solution after their stay in potassium chloride, are still much more permeable to potassium chloride than to sodium chloride, and that, as a consequence of this, they give up potassium chloride and water to the Ringer's solution. But perhaps the most interesting part of the result is the fact that so large a proportion of chlorine remains in the muscle after it has recovered its irritability. It is in the highest degree probable that the greater part of this chlorine left within the muscle fibers is combined with potassium. For the muscle fibers contain originally no other cation than potassium in sufficient quantity to combine with so much chlorine; and, if it were supposed that any

[4] In drawing conclusions from these experiments, the small amount of Cl found in fresh frog's muscle has been neglected. It amounts, according to Katz (Archiv für die gesammte Physiologie, 1896, lxiii, pp. 1, et seq.) to only 0.04 per cent of the weight of the muscle. It is probable that it comes chiefly from NaCl contained in the lymph spaces of the muscle, and that most of this NaCl is replaced by KCl under the conditions of Experiments 10 and 12.

considerable part of the chlorine in question came from sodium chloride, it would follow that this had diffused in from the Ringer's solution and that the fiber surfaces were, therefore, quite permeable to sodium chloride. Under these circumstances it would be difficult or impossible to account for the loss of chlorine and water by the muscle in the Ringer solution. We have, therefore, the paradoxical result that potassium chloride within the muscle fibers is less destructive to irritability than in the interstitial spaces.

The manner in which sartorii gain weight in 0.9 per cent potassium chloride solution. Figure 1 gives two curves showing the details of the manner in which muscle gains weight in 0.9 per cent potassium chloride solution. It will be noted that in both cases the gain is more rapid somewhere between the eighth and twelfth hours than during the preceding ones. It is doubtful how this peculiarity of the curves ought to be interpreted. The idea readily occurs to one that the surfaces of the muscle fibres may become progressively more permeable to potassium chloride throughout the course of the experiment and that this change may account for the more rapid swelling in the later periods. The results of Experiments 10 and 12, however, seem to point to a different interpretation. It is to be noted that in Experiment 12, in which the muscles were immersed for only three and a half hours in the potassium chloride solution, the chlorine contained by them made up 0.92 per cent of their increase in weight. In Experiment 10, on the other hand, in which the muscles were immersed for fourteen hours and a half in the potassium chloride solution the chlorine contained by them made up only 0.69 per cent of their increase in weight. These results must be taken with some caution, as the quantities of material used for the analysis were small; but they lend themselves readily to the supposition that, when muscle is immersed in an isotonic potassium chloride solution, the salt at first diffuses in rapidly and the water comparatively slowly. Under these circumstances the water intake would become more rapid at later stages of the experiment when the osmotic pressure within the muscle fibers was raised by the presence of considerable quantities of potassium chloride.

CONCLUSION

The changes which go on in muscle immersed in a 0.9 per cent potassium chloride solution are no doubt very complicated, and we do not feel that the experiments described in the preceding pages are nearly sufficient to give a satisfactory picture of them. The following inter-

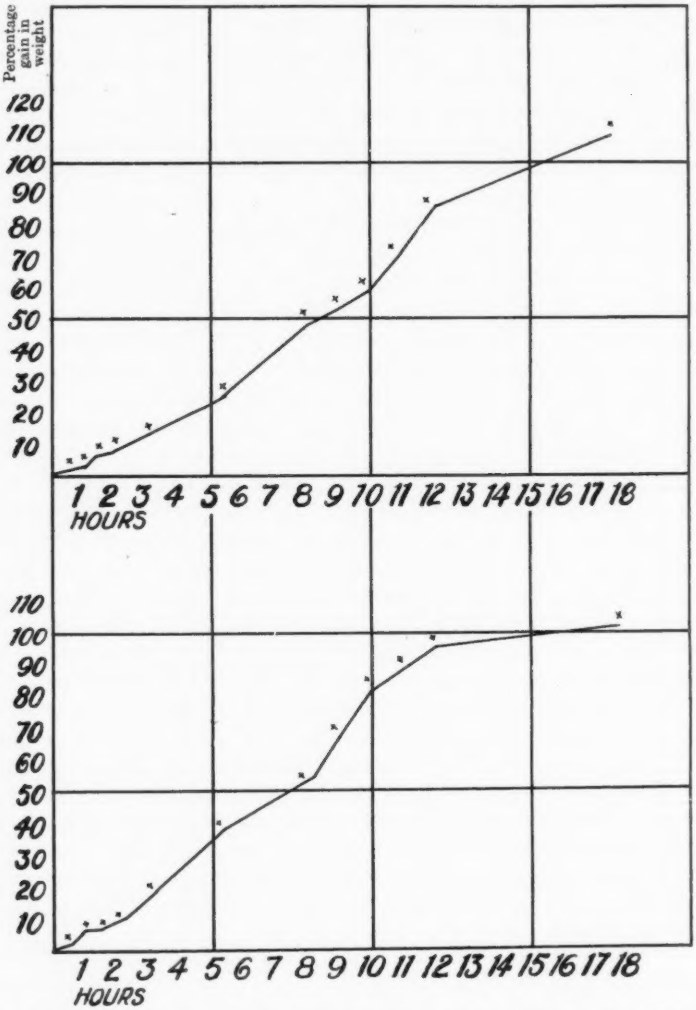

Fig. 1. Curves showing the manner in which frogs' sartorii gain weight in 0.9 per cent potassium chloride solution. Except at the periods of weighing, the muscles were kept in the ice box at between 5° and 10°.

pretation, however, appeals to us as that which fits best the facts so far known.

The surfaces of the normal living muscle fibers are decidedly more permeable to potassium chloride than to either sodium chloride or to the potassium phosphate normally contained within them. Consequently, when a muscle is immersed in an isotonic potassium chloride solution, the salt rapidly diffuses from the solution into the fibers and raises the osmotic pressure of their contents. As a result of this the fibers take up water also from the solution. The presence of potassium chloride in the interstitial spaces of the muscle temporarily destroys its irritability, as does that of any other potassium salt.

If such an experiment be carried out at a temperature above 19 degrees, the changes described cause the muscle to produce lactic acid in considerable quantities, and this prevents it from recovering its irritability when subsequently immersed in Ringer's solution. But if the experiment be carried out at lower temperatures, the lactic acid production is small; and the muscle may recover its irritability even after it has been for twenty-four hours in the potassium chloride solution and undergone a swelling which may amount to between 50 and 100 per cent of its original weight.

A small amount of calcium chloride added to the potassium chloride solution slows the pathological changes produced by the latter and increases the period during which the muscle remains alive, just as it does when added to a sodium chloride solution. It seems not improbable that the calcium acts in both cases to preserve the normal semi-permeable properties of the surfaces of the muscle fibers.

EXPLANATION OF THE EXPERIMENTS

The experiments recorded in the succeeding protocols were all carried out on frog's sartorii, which were immersed in the various solutions, and taken out, pressed against filter paper, and weighed at the intervals indicated. The technique of the drying on filter paper and weighing was in general the same as that described by Overton (Arch. f. d. ges. Physiol., 1902, xcii, p. 126). It is to be understood that each muscle remained in each of the various solutions from the time against which the solution is first mentioned until the time against which another solution is indicated. In Experiment I, for instance, the sartorius was immersed in Ringer's solution at 11.15 a.m. July 2, and remained in that solution until 2.25 p.m. At 2.25 p.m. it was found to weigh 0.223

gram, and immersed in 0.9 per cent KCl solution, where it remained until 8.30 p.m., when it was replaced in Ringer's solution. All the solutions were made up according to the method of Raoult; a "0.9 per cent KCl solution" means a solution made by adding 0.9 gram KCl to 100 cc. of distilled water; an "0.88 per cent KCl + 0.025 per cent $CaCl_2$ solution" means a solution made by adding 0.88 gram KCl and 0.025 gram $CaCl_2$ to 100 cc. of distilled water. The Ringer's solution used in Experiments 1 to 9 inclusive was made by adding 0.65 gram NaCl, 0.02 gram KCl, 0.025 gram $CaCl_2$, and 0.02 gram $NaHCO_3$ to 100 cc. distilled water. The Ringer's solution used in Experiments 10 to 13 inclusive was the same except that the $NaHCO_3$ was omitted. Our general experience, in addition to some preliminary experiments, which we have not thought it worth while to record in detail, lead us to believe that the survival of muscle under ordinary conditions and its recovery after treatment with KCl are litle affected by the presence or absence of $NaHCO_3$ in the Ringer solution used.

The weights of the muscles are given in grams, and, for convenience, the percentage changes in weight are given in the next column. The percentage changes are all calculated from the weight which each of the muscles had at the end of its first immersion in Ringer's solution.

During the intervals between weighings the solutions containing the muscles were kept in the ice box at temperatures which varied, as the protocols indicate, between 5 and 10°. In most cases the freshly removed muscles were placed immediately in the cold Ringer's solution. In Experiments 1, 2 and 3, as the protocols indicate, the freshly removed muscles were placed in Ringer's solution at 19°. The beakers containing the solution and the preparations were, however, immediately put in the ice box, and must have fallen to a temperature below 10° in the course of a few minutes.

In regard to the conventions used to indicate the degree of irritability of the preparations, it need only be said that "Irritability+" means that the muscle gave only a small contraction when stimulated by a strong current; "Irritability+++" means normal irritability; and "Irritability++," an intermediate degree.

In cases where one experiment is said to be a "control" or a "companion" for another, it is meant that the two experiments were carried out on the same day on opposite sartorii from the same frog.

Experiments 10 to 13 inclusive need no particular comment except that the chlorine estimations were made gravimetrically. As a control for our method of chlorine analysis we analyzed 2.073 grams of fresh

frog's muscle and found 0.058 per cent Cl. The figure given for the chlorine content of fresh frog's muscle by Katz (Arch. f. d. ges. Physiol., 1896, lxiii, 1 et seq.) is 0.0402 per cent.

PROTOCOLS OF THE EXPERIMENTS

Experiment 1. July 2 to 5, 1915

TIME	SOLUTION	WEIGHT	PERCENTAGE CHANGE IN WEIGHT	TEMPERATURE	REMARKS
July 2			*per cent*	°C.	
11.15 a.m.	Ringer			19	
2.25 p.m.......	0.9 per cent KCl	0.223		7	
8.30 p.m.......	Ringer	0.258	15.7	7	
July 3					
9.30 a.m.......	Ringer	0.221	−0.9	7	Irritability+++
July 4					
9.00 a.m.......	Ringer	0.215	−3.6	9	Irritability+++
July 5					
8.45 a.m.......	Ringer	0.211	−5.4	7	Irritability+++

Experiment 2. July 2 to 5, 1915

TIME	SOLUTION	WEIGHT	PERCENTAGE CHANGE IN WEIGHT	TEMPERATURE	REMARKS
July 2					
11.30 a.m.......	Ringer			19	
2.15 p.m.......	0.9 per cent KCl	0.231		7	
July 3					
7.30 a.m.......	Ringer	0.355	53.7	7	
12.07 p.m.......	Ringer	0.310	34.3	9	Unirritable
2.15 p.m.......	Ringer			9	Irritability+
July 4					
9.30 a.m.......	Ringer	0.261	13	9	Irritability++
July 5					
9.00 a.m.......	Ringer			7	Irritability++

Experiment 3. July 2 to 5, 1915

TIME	SOLUTION	WEIGHT	PERCENTAGE CHANGE IN WEIGHT	TEMPERATURE	REMARKS
July 2					
11.45 a.m.......	Ringer			19	
2.45 p.m.......	0.9 per cent KCl	0.215		7	
July 3					
2.45 p.m.......	Ringer	0.430	100	9	
July 4					
9.00 a.m.......	Ringer	0.275	28	9	Irritability+
July 5					
9.00 a.m.......	Ringer			7	Irritability+

Experiment 4. July 14 and 15, 1915

TIME	SOLUTION	WEIGHT	PERCENTAGE CHANGE IN WEIGHT	TEMPERATURE	REMARKS
July 14			*per cent*	°C.	
9.25 a.m.	Ringer			8	
11.25 a.m.	0.88 per cent KCl + 0.025 per cent $CaCl_2$	0.114		8	
3.25 p.m.	0.88 per cent KCl + 0.025 per cent $CaCl_2$	0.147	28.9	7	
5.25 p.m.	Ringer	0.157	37.7	7	
7.25 p.m.	Ringer	0.142	24.6	7	
9.25 p.m.	Ringer	0.125	9.6	7	
July 15					
9.25 a.m.	Ringer	0.127	11.4	7	Irritability+++

Experiment 5. Control for Experiment 4, July 14 and 15, 1915

July 14					
9.30 a.m.	Ringer			8	
11.30 a.m.	0.9 per cent KCl	0.107		8	
3.30 p.m.	0.9 per cent KCl	0.149	39.3	7	
5.30 p.m.	Ringer	0.163	52.3	7	
7.30 p.m.	Ringer	0.144	34.6	7	
9.30 p.m.	Ringer	0.127	18.7	7	
July 15					
9.30 a.m.	Ringer	0.130	21.5	7	Irritability++

Experiment 6. July 15 and 16, 1915

July 15					
2.35 p.m.	Ringer			7	
July 16					
10.05 a.m.	Ringer	0.114		8	
11.05 a.m.	0.9 per cent KCl	0.110		8	
2.05 p.m.	0.7 per cent NaCl	0.125	13.6	6	
2.35 p.m.	0.7 per cent NaCl	0.126	14.5	7	
3.35 p.m.	0.7 per cent NaCl	0.126	14.5	7	
5.30 p.m.	0.7 per cent NaCl	0.126	14.5	7	Irritability++

Experiment 7. Control for Experiment 6, July 15 and 16, 1915

TIME	SOLUTION	WEIGHT	PERCENTAGE CHANGE IN WEIGHT	TEMPERATURE	REMARKS
July 15			*per cent*	°C.	
2.30 p.m.......	Ringer			7	
July 16					
10 a.m..........	Ringer	0.109		8	
11 a.m..........	0.9 per cent KCl	0.114		8	
2 p.m..........	Ringer	0.135	18.4	6	
2.30 p.m.......	Ringer	0.136	19.3	7	
3.30 p.m.......	Ringer	0.132	15.8	7	
5.30 p.m.......	Ringer	0.130	14.0	7	Irritability+++

Experiment 8. July 15 and 16, 1915

July 15					
2.45 p.m.......	Ringer			7	
July 16					
10.15 a.m.......	Ringer	0.99		8	
11.15 a.m.......	0.9 per cent KCl	0.102		8	
2.15 p.m.......	0.7 per cent NaCl	0.110	7.8	6	
2.45 p.m.......	0.7 per cent NaCl	0.107	4.9	7	
3.45 p.m.......	0.7 per cent NaCl	0.107	4.9	7	
5.45 p.m.......	0.7 per cent NaCl	0.109	6.9	7	Irritability++

Experiment 9. Control for Experiment 8, July 15 and 16, 1915

July 15					
2.40 p.m.......	Ringer			7	
July 16					
10.10 a.m.......	Ringer	0.098		8	
11.10 a.m.......	0.9 per cent KCl	0.094		8	
2.10 p.m.......	Ringer	0.107	13.8	6	
2.40 p.m.......	Ringer	0.108	14.9	7	
3.40 p.m.......	Ringer	0.102	8.5	7	
5.40 p.m.......	Ringer	0.101	7.4	7	Irritability+++

Experiment 10. July 21 and 22, 1915

10.35 to 11.30 a.m. Sartorii from 5 frogs (one from each frog) dissected out and placed in Ringer's solution at 8 to 9°.

11.30 p.m., July 21 to 12.15 a.m. July 22. These muscles found to weigh 0.857 gram; transferred to 0.9 per cent KCl solution.

2.15 to 3.05 p.m., July 22. These muscles weighed 1.520 grams. They were fused with Na_2O_2 and analyzed for Cl. They yielded 0.0188 gram AgCl, equivalent to 0.0046 gram Cl, or to 0.0097 gram KCl.

Experiment 11. Companion to Experiment 10, July 21 to 23, 1915

10.35 to 11.30 a.m. The other sartorii from the frogs used in Experiment 10 were dissected out and placed in Ringer's solution at 8 to 9°.

11.30 p.m., July 21, to 12.15 a.m., July 22. These muscles were found to weigh 0.871 gram; they were transferred to 0.9 per cent KCl solution.

2.15 to 3.05 p.m., July 22. These muscles weighed 1.610 grams; transferred to Ringer's solution.

9.30 to 9.50 a.m., July 23. These muscles weighed 0.985 gram; all found to be moderately irritable. They were fused with Na_2O_2 and yielded 0.0107 gram AgCl, equivalent to 0.0026 gram Cl, or to 0.0055 gram KCl.

Experiment 12. September 8, 1915

11.37 a.m. to 12.15 p.m. Sartorii from 6 frogs (one from each frog) removed and placed in Ringer's solution at 8 to 9°.

4.45 to 5.40 p.m. These muscles found to weigh 1.054 grams; transferred to 0.9 per cent KCl solution.

8.15 to 9.10 p.m. These muscles weighed 1.337 grams. They were fused with Na_2O_2, and yielded 0.0106 gram AgCl, equivalent to 0.0026 gram Cl, or to 0.0055 gram KCl.

Experiment 13. Companion to Experiment 12, September 8 and 9, 1915

11.37 a.m. to 12.15 p.m., September 8. The other sartorii from the frogs used in Experiment 12 were dissected out and placed in Ringer's solution at 8 to 9°.

4.45 to 5.40 p.m. These muscles found to weigh 1.067 grams; transferred to 0.9 per cent KCl solution.

8.15 to 9.10 p.m. These muscles weighed 1.344 grams; transferred to Ringer's solution.

10.00 to 10.34 a.m., September 9. These muscles weighed 1.140 grams. One was only slightly irritable; all the rest were moderately irritable. They were fused with Na_2O_2 and yielded 0.0088 gram AgCl, equivalent to 0.0022 gram Cl, or to 0.0047 gram KCl.

REFERENCES

(1) Overton: Arch. f. die gesammt. Physiol., 1904, cv, 199.
(2) Siebeck: Ibid., 1913, cl, 316.
(3) Meigs: Journ. Exper. Zool., 1912, xiii, 518.
(4) Meigs: Loc. cit., Experiments 72 and 77.
(5) Siebeck: Loc. cit., Experiment 4.
(6) Loeb: Biochem. Zeitschr., 1911, xxxii, 320; also Meigs: This Journal, 1915, xxxvii, 456.
(7) Overton: Arch. f. die gesammt. Physiol., 1902, xcii, 128.
Meigs and Ryan: Journ. Biol. Chem., 1912, xi, 410.
Meigs: Ibid., 1914, xvii, 91.
Meigs: Ibid., 1915, xxii, 494.

THE INFLUENCE OF AGE UPON THE VENOUS BLOOD PRESSURE IN MAN

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In the course of observations directed to other ends it was noted that the venous blood pressure was appreciably lower in boys than in men of mature years. Accordingly, when opportunity offered in the summer of 1915, a series of observations on men of different age groups were collected and are reported in this paper.

The method used has been described elsewhere (1). Because of the uncertainties of illumination the pressures were read at complete collapse of the vein and not, as is more accurate, at the point at which the shadow comes and goes with slight oscillations of the outside pressure. This tends to give somewhat higher values but under the present circumstances the comparative value of the pressures is undoubtedly more reliable. In collecting the data all obviously abnormal cases, particularly in regard to cardiac lesions, were excluded. The children were found in orphan asylums and in schools; the boys in schools and shops; the young men in colleges and shops; the men in shops and the old men in institutions for the aged. Several of the groups were completed with ambulatory surgical cases in the dispensary and hospital. In all cases the observations were made in the trunk-vertical position.

The accompanying figure (fig. 1) presents the data obtained. The venous pressure readings, expressed in centimeters of water and referred to the heart level, are plotted on the abscissae and the ages of the subjects on the ordinates. The average of all the readings in the several decades in which not less than fifty observations were made are presented in the form of a curve. These average figures are as follows:

YEARS	CM.	YEARS	CM.
5–15	8.30	45–55	19.04
15–25	12.66	55–65	24.17
25–35	15.00	65–75	25.59
35–45	17.98	75–85	26.00

These values show clearly that there is a continuous rise in venous pressure as age progresses. If, however, averages are made for the half-decades in which not less than twenty-five observations were made, the rise of pressure is less regular as the following figures show.

YEARS	VENOUS PRESSURE	INCREASE IN PRESSURE OVER PRECEDING HALF DECADE
	cm.	
5-10	6.36	–
10-15	9.97	3.61
15-20	11.58	1.61
20-25	13.39	1.81
25-30	13.88	0.49
30-35	16.08	2.20
35-40	17.22	1.14
40-45	18.80	0.58
45-50	17.85	−0.95
50-55	20.28	2.43
55-60	24.03	3.75
60-65	24.29	0.26
65-70	24.27	−0.02
70-75	26.44	2.17
75-80	26.11	−0.33
80-85	25.88	−0.23

A curve plotted from these figures shows irregularities between 25 and 30, 45 and 50, and 60 and 70 years. I am not inclined to stress these irregularities because it is not improbable that they would be smoothed out if the number of observations was increased. It will be seen that the maximum pressure occurs between 70 and 75 years and that the averages for the two half-decades following are both lower. Whether there is any significance in this drop of venous pressure toward the end of life may be doubted but the fact that it appears to prevail over a number of years suggests that it may be indicative of the failure of some compensatory mechanism.

Clark (2) found in a study of cardiac cases that a venous pressure persisting and rising above 20 cm. foretold the approach of clinical signs of decompensation and that such a condition, in patients confined to bed, usually indicated a fatal outcome. His cases ranged around 50 years of age for which age the normal average pressure, as here given, is 19.04 cm. It is inconceivable that the healthy individuals in my series should exhibit a venous pressure so close to the danger zone as

noted by Clark. Clark's criterion for reading the pressure was the point at which the shadow of the vein comes and goes with slight oscillations of the outside pressure which is more accurate and gives lower values than the criterion which I was obliged to employ, namely, the

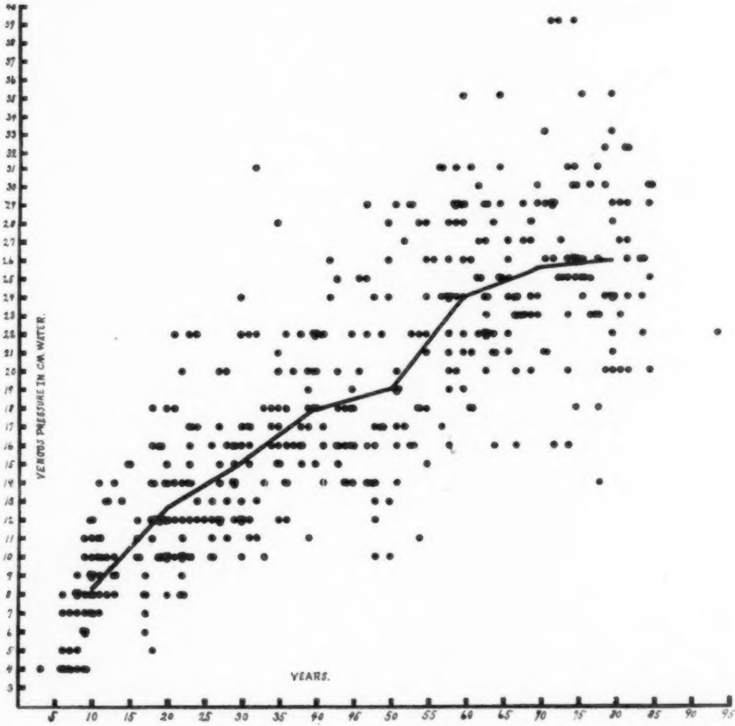

Fig. 1. Venous blood pressure observations on men. To show the rise in venous pressure which occurs as age progresses. The dots represent individual observations. The curve represents the average of not less than fifty observations in each of the several decades.

point of complete collapse of the vein. This difference in method might give values differing a couple centimeters. Furthermore, my subjects were up and about and active, Clark's cases were confined to bed in a semi-recumbent position. It is not known what effect protracted quiet has on the venous pressure but it is probably safe to assume that it

would result in lowered values. Finally, Clark's cases presumably had some myocardial weakness, the result of which might well be that the heart was unable to function under a feeding pressure that in normal individuals causes no embarrassment whatsoever. It would seem, therefore, that the results here reported are not necessarily in conflict with Clark's conclusion that a pressure of 20 cm. in cardiac cases is dangerous.

The figure shows profound variations in the venous pressure in all periods of life. Doubtless every healthy individual exhibits a normal variation attributable in part to the condition of bodily activity and to the diurnal rhythm (1). In the series of observations here reported the first of these could not well be controlled and no correction for the second was made. That there are still other factors contributing to normal variations in venous pressure may be assumed but they have not been investigated. Allowing, however, for these normal variations, it is probable that still other causes must be invoked to account for the extreme differences found in each age period. Probably the ages given by the subjects are in the main reliable except in the case of the very old in whom there appeared to be a tendency to in-accurate statement. The resistance of the skin and the rigidity of the venous wall would obviously influence the amount of pressure required to collapse the vein but the few cases exhibiting such conditions were excluded. The most probable cause of these extreme variations would seem to lie in the condition of bodily health, the relation of which to venous pressure, except in cardiovascular cases, is as yet unknown. Effort was made, as has been stated, to exclude from the series all but healthy individuals, but in a large series poorly under control and in which only the grossest condition of general health was established it seems not improbable that numerous abnormal conditions might go undetected which would be capable of causing at least some of the extreme variations in pressure observed.

The factor or factors contributing to this age-rise of venous pressure are unknown. Casual inspection of animals suggests that the pressure may vary directly with the size or weight of the body. If we assume that man has reached maturity at 40 years and thereafter does not gain in size or weight (3) we may be justified in considering the first part of the present curve of venous pressure as an expression of growth. The curve of growth shows a fairly constant rise until 17 years is reached and thereafter flattens, at first slowly then more rapidly until 40 years. In a general way the curve of venous pressure exhibits a similar trend.

After this period the curve of venous pressure is less regular although the rise persists. The suggestion that this later rise represents a functional compensation for the weakened heart muscle of age is attractive but too many other changes in the cardio-vascular mechanism are involved to warrant any but the most qualified consideration of the suggestion.

It is interesting to note that young men in exercise may raise their venous pressure to the height found in old men at rest as the following figures show:

AGE	BEFORE EXERCISE	AFTER EXERCISE
	cm.	*cm.*
26	8	26
19	12	24
20	15	24
20	10	24
39	11	28
29	—	32

The first value given was obtained before and during exercise on a stationary bicycle; the others were obtained before and some minutes after a competitive five-mile run. While these figures doubtless do not represent the maximum venous pressure which the human heart can sustain they bear a striking relationship to the values found in old age, a relationship which suggests a common causative factor.

Finally, a possibility to account for the progressive rise in venous pressure in the later years of life is a change in position of the right auricle with respect to the subcostal angle. One gets the impression on palpating for the subcostal angle that it lies lower on the trunk in old people. This may be due to a bony rigidity which defines the point of palpation more sharply and at a lower level than in the young. If such a condition exists it would lead to higher pressure readings. But it is generally stated that the thorax assumes a more conical form as years pass and it is also stated that the base of the heart is lower in old people than in younger ones (4). If these statements are accepted the pressure readings would tend to be lower, so it would seem that any change in the assumed position of the heart, if one exists, in people of different ages must be ascribed to differences in rigidity of the thorax. Such rigidity and the expansion of the lower part of the thorax would

increase the prominence of the tip of the sternum, thereby giving a lower point of palpation. Such differences cannot, however, be great enough to account for all of the rise in venous pressure noted in old people.

CONCLUSIONS

Observations on the venous blood pressure in men of different ages are presented which show a progressive rise in venous pressure practically throughout life.

REFERENCES

(1) Hooker: This Journal, 1914, xxxv, 73.
(2) Clark: Arch. Int. Med., 1915, xvi, 587.
(3) Minot: Age, Growth and Death, New York, 1908, p. 99.
(4) Dietlen: Ergebn. d. Physiol., 1910, x, 598.

THE CHIEF PHYSICAL MECHANISMS CONCERNED IN CLINICAL METHODS OF MEASURING BLOOD PRESSURE[1]

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This paper attempts to analyze the chief physical mechanisms concerned in clinical methods of measuring systolic and diastolic blood pressure with the use of an arm band or plethysmograph, where the arm band is inflated to a high pressure until the radial pulse is suppressed, and then is gradually lowered until the radial pulse reappears. This is taken as the systolic pressure. Or else graphic tracings are taken of the pressure in the arm band, so that when the pressure is high in the arm band no oscillations in the tracing are produced by the heart beat. But as the pressure in the arm band is gradually lowered a point is reached where arterial pulsations are feebly transmitted through the cuff pressure and appear in the tracing. This point was formerly taken by many as the systolic pressure. At a somewhat lower level the tracing often shows a more rapid augmentation of the arterial pulsatory oscillations and often it also shows at about this point a widening of the limbs and also somewhere near this point there is often noted a notch in the downward limb. The various points are taken by others to be the systolic pressure. From these levels on down, as the arm band pressure is gradually lowered, the arterial pulse waves recorded on the tracing are augmented until they reach the maximum. Some point on this maximal oscillation, or else the first diminished beat is the most commonly selected criterion for obtaining the diastolic pressure. How-

[1] A preliminary report of this work was made in 1914 at the St. Louis meeting of the American Physiological Society. Also some of the results were presented in a paper read before the Allegheny County Medical Society, February 16, 1915, a brief abstract of which was published in the Bulletin of that society. The later results were presented before the 1915 meeting of the American Physiological Society at Boston.

ever, all do not agree. As the arm band pressure is still further lowered, the tracings of arterial pulsation gradually diminish and finally disappear. Another series of criteria for locating the systolic and diastolic blood pressures are certain of the various phases of sounds produced and heard through a stethoscope when the arm band is compressing the artery at different levels of pressure.

The results of the present study lead to the conclusion that none of these various above described commonly accepted criteria for obtaining the systolic and diastolic blood pressures yield correct measurements, but give readings which are too high. The amount of error depends upon and varies directly as the resistance of the arterial wall to compression and distension.

This means, among other things, that the results show that the greatest pulsatory oscillations obtained from a plethysmographic tracing of a finger or limb, or from an arm band are not obtained when the counterpoise pressure is exactly equal to the diastolic pressure, in other words, that the commonly accepted principle of Marey (1) does not hold. Marey argued that in this state the blood vessels would be completely relaxed so that their walls would fluctuate freely as if floating passively between the pressures of the blood within the vessel and that of the counterpoise pressure without the vessel. But we hold that Marey's principle is not true even provided the oscillations of blood pressure be infinitely small, or that the movement of mercury in the manometer be infinitely small or that the dilation of the vessel during systole be infinitely small. For, we argue, the moment the blood pressure begins to rise above the diastolic, at once the blood vessel must begin to be distended. This distention must be sufficient to allow the displacement necessary to fill the space in the mercury manometer caused by the elevated pressure. Therefore, necessarily, the instant the blood pressure begins to rise above the diastolic, there will be interference with the transmission of the arterial pulse wave, or the transmitted oscillation will be damped by the stretched blood vessel. As a matter of fact, the most favorable point for the transmission of extremely minute arterial oscillations of pressure is where the vessel is in a partially collapsed condition, for here is possible the easiest fluctuation in volume with the least bending of the walls of the vessel. The sides of the vessel in this condition are not flattened but are curved (fig. 8, *B*). So Marey's principle is not true even under theoretical conditions.

It is upon the Marey principle that the most commonly accepted

clinical methods of measuring diastolic blood pressure rest, for as mentioned above, the practice is to take as the criterion of diastolic pressure the lowest point on the greatest oscillation or the first beat where the amplitude of the oscillations begins to decline. Likewise, until very recently critical scientific opinion has been almost as overwhelming in favor of the Marey principle. However, some have not accepted it. For example, Martin (2) advocated raising external pressure till diminution occurred, and then lowering it till diminution occurred and that the average be taken as the mean blood pressure. Also, Mosso (3) thought he measured the mean pressure by taking the mean point on the greatest oscillation (instead of the lowest point). Roy and Adami (4) claimed the true diastolic pressure was slightly (4 to 5 mm. of mercury) below that of the point of greatest oscillations. Hill and Bernard (5) took the lowest point of the greatest oscillation to be the mean blood pressure. Oliver (6) held that the greatest oscillations occur at the mean blood pressure. The excellent work of MacWilliam and Melvin (7) was not seen by us until our work was about half completed. They found that the greatest oscillations occurred at a point where the counterpoise pressure was raised sufficiently above the true diastolic to cause the blood vessels to be completely flattened at the diastolic level. But when using a larger rubber tube it was observed to be only half flattened at the diastolic level. They did not explain why this was so. Our results offer an explanation for the apparent discrepancy. Wiggers (8) calls attention to interesting work by Christen (9). However, we have been unable to obtain access to the original publication.

PLAN OF EXPERIMENTATION

The plan of experimentation adopted was to use the simplest possible physical models to work out the underlying physical principles involved in the process of making clinical blood pressure measurements with the arm band or plethysmograph. Complicated models with artificial heart, aorta, other vessels, peripheral resistance and artificial heart beat of normal rate and circulatory fluid in motion, were thought to make difficult the recognition and analysis of the processes going on. The pressure was controlled by raising and lowering pressure bottles. These changes in pressure which were graphically recorded were made accurately and slowly enough to permit the easy analysis of the results.

The sounds produced were studied and the mechanism of their production ascertained as completely as possible at this time.

After the physical experiments were fairly well advanced a series of experiments on the dog were performed according to the following plan: The dog's own heart beat was stopped but the pressure curve in the aorta was maintained artificially by a supply of warm 0.9 per cent NaCl mixed with blood. It was so arranged that pulsations were made from a certain known and controlled minimum or diastolic pressure up to a certain known and controlled maximum or systolic pressure. The pulsations were made slowly enough to permit easy analysis of the tracings. In this way the pressure curve in the aorta was a known quantity. Readings by the arm band method were then made and compared with the actual pressure.

The results of the physical experiments were found to be applicable to and in agreement with those of the animal experiments.

EXPERIMENTAL RESULTS

A good many physical experiments of a very elementary character were performed which are not included in this paper for the reason that they are already well known and they do not bear directly on the problem under investigation here. Even some that are reported here are not offered as new or original; but they are given in order to form a foundation for the explanation and illustration of what takes place when the blood pressure is measured by the arm band method.

The volume pressure curve of a rubber membrane was tested. A thin piece of rubber tissue was stretched lightly over the mouth of a thistle tube which was inserted upward through the bottom of a two-holed rubber stopper. A glass tube was inserted through the other hole in the rubber stopper. The stopper was inserted into a wide mouthed bottle. The outer end of the thistle tube was then connected with a pressure bottle which also communicated with a mercury manometer which traced on a kymograph. The other glass tube was fitted with a narrow nozzle tip and bent down to discharge into the top of a burette.

The zero point was obtained by filling the whole system with just the amount of water so that the tip of the discharging nozzle just dipped under water in a beaker, while the level of the top of the water in the pressure bottle was on a level with that of the water in the beaker, and with the rubber diaphragm completely relaxed and the pressure equalized on each side of it. Then the beaker of water was removed and at the same time the pressure bottle was very slightly lowered to the level of the opening of the nozzle. The curve of volume as a func-

tion of pressure was then taken either by successively raising the bottle a certain distance, or else by successively raising it gradually until a certain volume of water had been discharged into the burette (fig. 1).

The results of these experiments are shown in the curve in fig. 2. In studying the curve it is seen that at first when pressure is brought on the membrane it gives way easily and a relatively slight change in pressure causes a large fluctuation in volume. This results in a bulging of the membrane which is gradually stretched assuming a more and

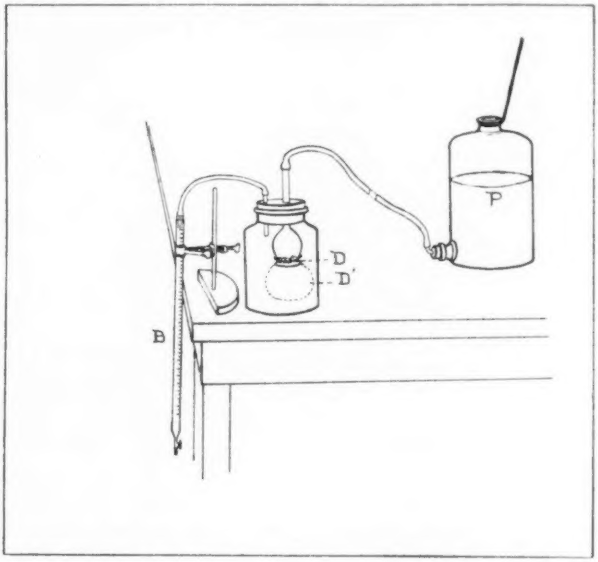

Fig. 1. Arrangement of apparatus for obtaining volume pressure curve of rubber diaphragm. *P*, pressure bottle; *B*, burette; *D*, rubber diaphragm relaxed; *D'*, rubber diaphragm distended.

more convex shape. As this occurs there is a diminution of the rate of volume change as compared with the rate of pressure change. So the volume-pressure curve bends upward. After a time, when the membrane is so far bulged outward that it assumes a more rounded shape, the relation alters so that the volume increases more rapidly than the pressure does. Still later, when the walls of the membrane have become so thinned that they form a large sphere attached at one side to the thistle tube, the pressure does not need to increase any further

in order to produce a further increase in volume. In short, the now large rubber balloon would burst if kept under that constant pressure. It has reached the blow-out phase. In this state, it is like the urinary bladder and other physiological spherical sacs, which when they are

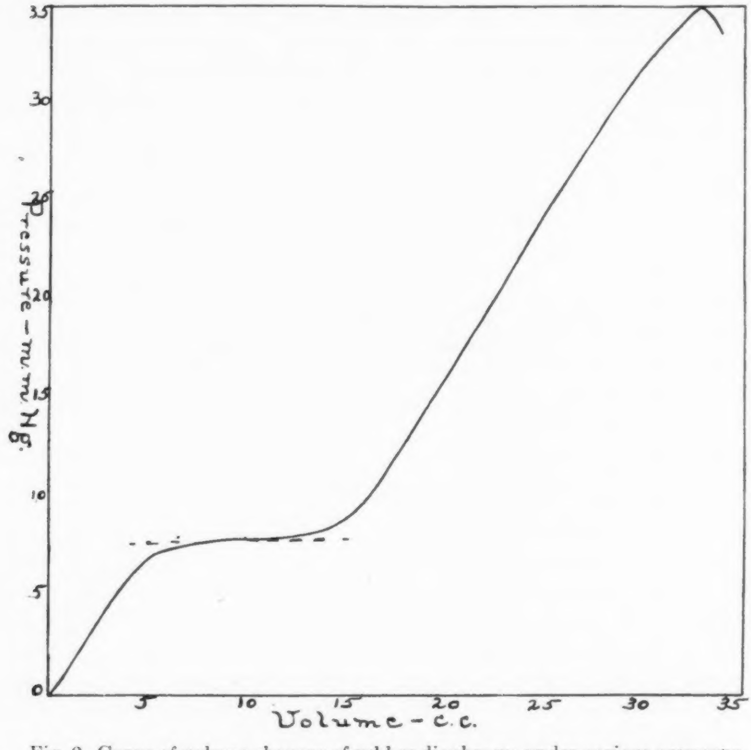

Fig. 2. Curve of volume changes of rubber diaphragm under various pressures. - - - - - Level where inside and outside pressures are equal.

well filled, but not over distended, have no higher pressure than when partially filled.

This line of experimentation prepares us for the results given below that when we seek to measure a curve of pulsatory pressure on the one side of a membrane by taking a tracing of the oscillations transmitted by this pressure to the space on the other side of the membrane we get

the following result: By using the same apparatus as in figure 1, but connecting a recording manometer in place of the narrow tipped nozzle and connecting also a pressure bottle in this system, oscillations of pressure can be made on one side of the membrane which are transmitted to the other side. One side we elect as representing the inside or arterial pressure, the other will be the outside or arm band pressure (fig. 3).

Now, after having placed the inside pressure bottle at diastolic level, if the outside pressure bottle is raised to a high point, the mem-

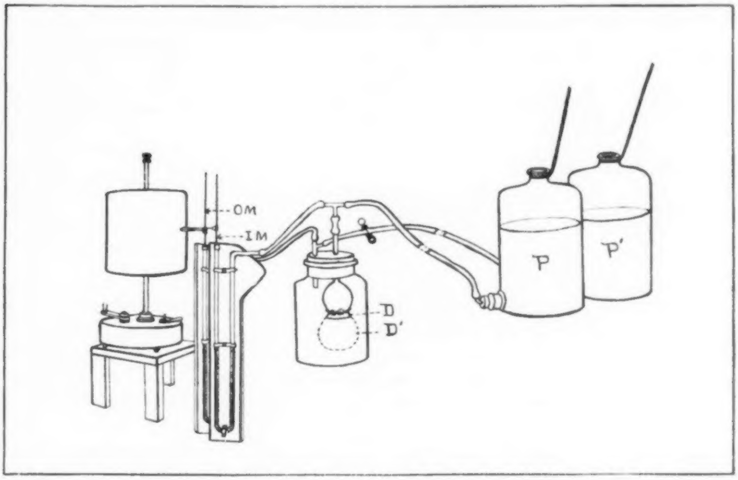

Fig. 3. Arrangement of apparatus for recording height of oscillations made on one side of rubber diaphragm and the resulting transmitted oscillations. *P*, inside pressure bottle; *P'*, outside pressure bottle; *IM*, inside manometer; *OM*, outside manometer; *D*, rubber diaphragm collapsed; *D'*, rubber diaphragm distended.

brane bulges in and adapts itself to the inside of the thistle tube. In this state, if the inside pressure bottle is raised from the diastolic to the systolic level, there will be only a slight wave of the pulsatory pressure transmitted to the outside manometer for the stretched membrane applied against the inside of the thistle tube prevents it. Now the outside pressure is gradually lowered and the transmitted pulse oscillations increase until they reach a maximum. This maximum is reached at the point where the *mean* of the *inside* pulsatory pressure

is just equal to the *mean outside* pressure. In short, the membrane offers less resistance to the pulse wave when the inside pressure is just equal to the outside pressure. And in order to reduce the damping effect of the membrane to the lowest limit, any given pulse oscillation must swing equally above and below this favorable point (fig. 4, *A*). If we start with the *diastolic point* of *inside* pressure just equal to the *diastolic point* of *outside pressure*, (which ought to produce maximal oscillations according to Marey's principle), the oscillations transmitted and recorded on the tracing by the outside manometer are not so great as they were in the above experiment. The reason for this is that the membrane is at a favorable point of complete relaxation at the beginning of the pulse wave, but it must become more and more stretched as the pressure rises above the diastolic level (fig. 4, *B*). The reverse is true when the *inside pressure* at *systolic* level is just balanced by the

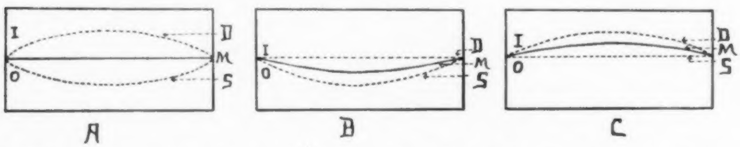

Fig. 4. Diagram showing movements of rubber diaphragm caused by oscillations in pressure. *I*, inside pressure space; *O*, outside pressure space; *A*, when mean inside and outside pressures are equal; *B*, when diastolic inside and outside pressures are equal; *C*, when systolic inside and outside pressures are equal; *D*, *M*, *S*, position of rubber diaphragm at diastolic, mean and systolic pressures.

systolic point of *outside* pressure. Here again, the transmitted oscillations are not so great as those where the mean inside pressure is just equal to the outside pressure (fig. 4, *C*).

Therefore, where the *mean inside pressure* is just equal to the *mean outside* pressure is the *most favorable point* for the transmission of pulsatory waves through a rubber diaphragm, and therefore, it is the point of greatest transmitted pulsatory oscillations.[2]

Although the above principle is true for a rubber membrane which is flat and which under high pressure bulges out and becomes spherical in shape, it does not follow that it must be true for a rubber tube or for blood vessels, which are cylindrical in shape.

The curve of volume pressure of a rubber tube of a thinness and a soft-

[2] This is true within the lower limits of the elasticity of the diaphragm. If the inside diastolic pressure is so great as to distend the diaphragm into a spherical balloon with thin walls, this law is altered. But that need not be discussed in this paper.

ness rather similar to that of a large blood vessel was taken in the same manner as was the curve for the diaphragm described above. The curve is different from that of the rubber diaphragm. That is, the volume-pressure curve of the rubber tube, within the limits of pressure used, passes through three phases (fig. 5).[3] The first phase is where

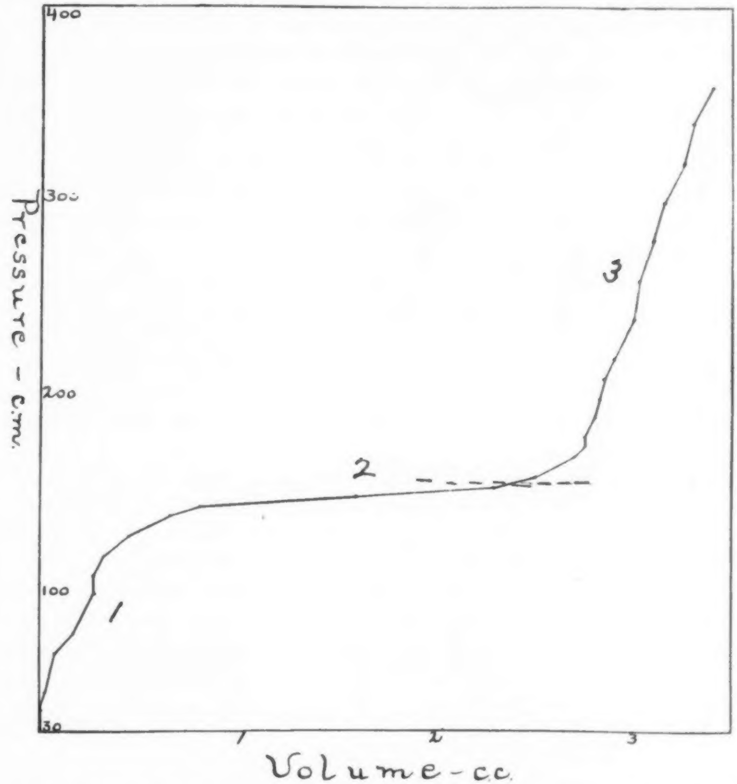

Fig. 5. Curve of volume change of rubber tube under various pressures. *1*, first phase; *2*, second phase; *3*, third phase;- - - - level where inside and outside pressures are equal.

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[3] If the inside pressure were increased to the bursting point of the tube the curve would be altered as was the case in the rubber balloon phase of the diaphragm experiment, but this need not be entered into here, because it is not encountered in taking blood pressure readings.

the outside pressure is sufficiently higher than the inside to cause the vessel to be collapsed. Here a given increase in pressure inside the tube gives the least change in volume because the vessel is more or less completely collapsed and the transmission of pressure is damped by the outside pressure which holds the tube more or less tightly shut. In the second phase there is the greatest change in volume with a given change in pressure because the vessel merely changes in shape from the collapsed, flat closed to the passively rounded, open. This does not require stretching of the walls of the vessel, but only requires bending of them. In the third phase the tube is open and round. An increase in volume requires increase in circumference of the tube. This requires that the walls of the rubber tube be actually stretched; not merely bent. So here, as in the first phase, the increase in volume is small with a given increase in pressure; but it is not as small as in the first phase.

Other conditions being equal, the smaller the calibre of the tube, the greater are the differences between the three phases of the curves.

Next in order is the consideration of the transmission of pulsatory oscillations made by the inside pressure and recorded by the outside pressure. The arrangement of the apparatus is shown in figure 6. It is similar in principle to that described above for the rubber diaphragm experiment.

Beginning with the outside pressure at so high a point that the rubber tube was flatly collapsed thereby, oscillations of the inside pressure were made slowly and accurately by raising and lowering the inside pressure bottle. A level was arbitrarily selected as the diastolic pressure, and another level conveniently located above it was arbitrarily taken for the systolic pressure. In this way the pulse oscillations throughout the experiment were controlled and kept at the same level. They were made slowly and steadily so that the tracing would be accurate.

The results of this series of experiments are as follows: Beginning with the outside pressure at quite a high level and making pulsatory oscillations in the inside pressure from the diastolic to the systolic level it was found that very tiny oscillations were transmitted to the outside manometer. It was very difficult to raise the outside pressure to such a great height that no oscillations whatever were transmitted. In other words, the point where the oscillations first appeared was far above the true systolic pressure. *The height above the systolic at which*

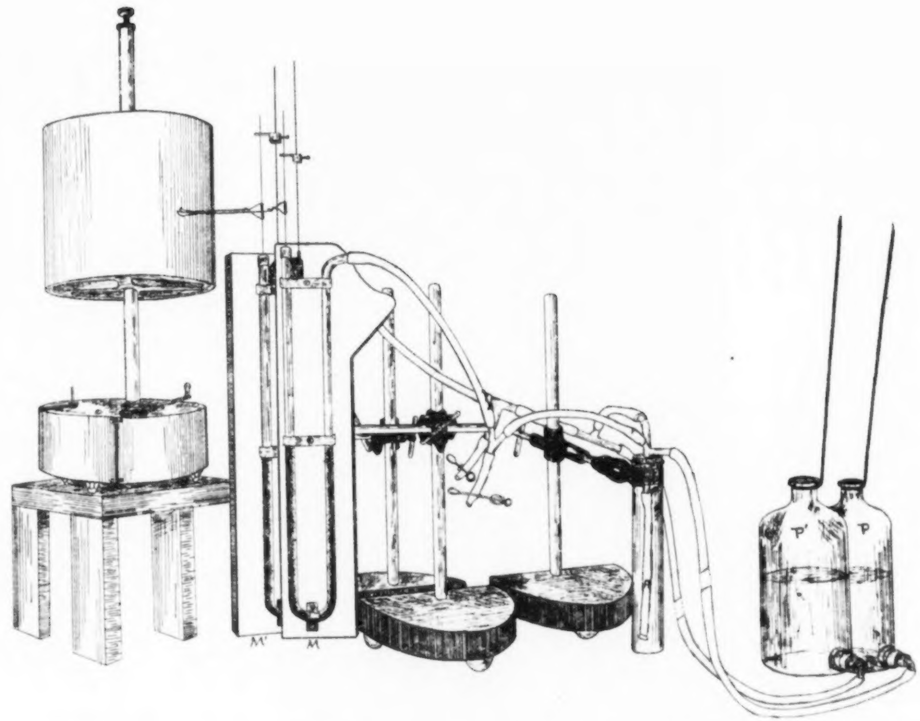

Fig. 6. Apparatus arranged for producing and recording inside (arterial) pressure oscillations and the resulting transmitted outside (arm band) pulsatory oscillations. *A*, artery or rubber tube; *P*, arterial or inside pressure bottle; *P'*, arm band or outside pressure bottle; *M*, arterial or inside manometer; *M'*, arm band or outside manometer.

they first appeared varied directly as the delicacy of the tracing mechanism, and also directly as the resistance of the vessel.

Then, as the pressure in the outside system, or as the outside pressure bottle was lowered, the transmitted pulsations were correspondingly gradually augmented until they reached a maximal. *This point of maximal pulsations however, was at a much higher level than the true diastolic pressure.*

As the outside pressure bottle was further lowered there was adecrease in the transmitted oscillations until they became very small.

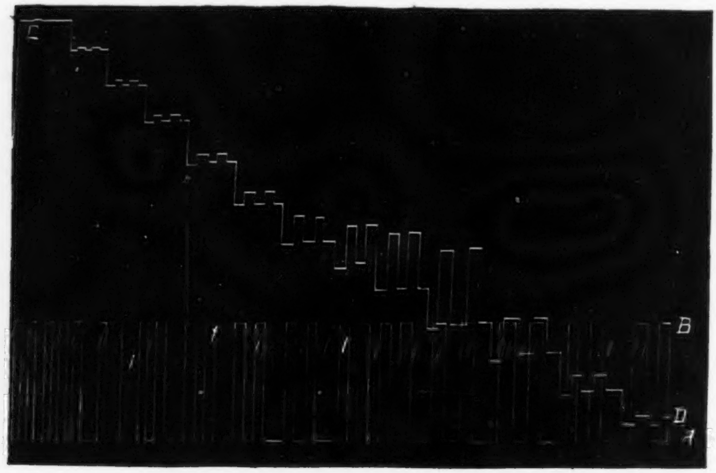

Fig. 7. Tracing showing transmitted pulsatory oscillations made by inside pressure and recorded by outside pressure. *A–B*, actual oscillations inside of rubber tube; *C–D*, transmitted oscillations.

And, like those small oscillations seen when the outside pressure was extremely high, it was very difficult to reach a point where they disappeared completely, and also like them, the point to which they descended varied directly as the delicacy of the tracing mechanism.

Figure 7 shows a typical tracing taken as just described. Note that in this instance, even the lowest point of the greatest oscillations is at a point not only above the diastolic, but even above the systolic pressure.

The alterations in the shape of the vessel or the rubber tube during the taking of this tracing are interesting and significant. In the ordi-

nary experiments with our model, at the highest point on the tracing where the outside pressure is high above the inside pressure, the tube is completely collapsed, except when there are two little spaces, one at each corner of the flattened tube, which are not completely closed (fig. 8, *A*). These unclosed spaces at each corner open slightly when the inside pressure rises from diastolic up to systolic level. As the outside pressure is lowered these spaces increase in size until they attain a size where the arterial tube opens very slightly when the inside pressure reaches systolic level (fig. 8, *B*). As the outside pressure is still further lowered, the arterial tube continues to open wider until it reaches the point where the greatest transmitted oscillations are traced. At this level, at the diastolic pressure the arterial tube is more or less completely collapsed, at the mean pressure the tube has become about half collapsed and at systolic pressure it has rounded and filled out and then become slightly stretched (fig. 8, *C*). The degree of fluctuation depends

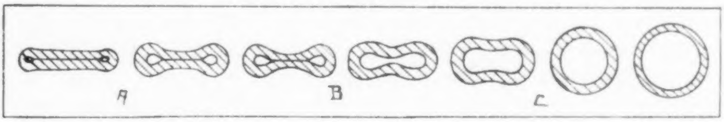

Fig. 8. Cross-section of vessel or rubber tube showing changes in shape during oscillations of pressure. *A*, when outside pressure is high above inside pressure, tube completely or almost completely collapsed. *B*, outside pressure lower than *A*, vessel partly open; *C*, outside pressure still further lowered.

upon the ratio of volume of the arterial tube to the volume of the manometer.

Here, as with the diaphragm experiment, there is a favorable point where oscillations are most readily transmitted. It is not at the point where mean inside pressure exactly equals mean outside pressure, because the curve of volume-pressure of the rubber tube is not the same above this point as it is below it. In this regard it does not behave like the rubber membrane. For within limits it is more difficult to expand the rubber tube more completely above the favorable point than it is to collapse it more completely. Therefore, in order to compensate for this inequality in the tube's curve of pressure, the greatest oscillations may be obtained if, when beginning the tracing, the mean of the outside pressure be elevated above the mean of the arterial or inside pressure. Just how much of this compensatory elevation is necessary depends upon (1) the pressure-volume curve of that partic-

ular arterial tube; (2) upon the amplitude of the inside pulsatory oscillations; and (3) upon the volume of displacement necessary in the outside mercury manometer in order to accommodate itself to the change of pressure.

That is (1) the larger the calibre and the thinner and softer the walls of the tube, the more the curve of volume pressure would be extended, and therefore, a slight change in pressure would cause a great increase in volume, or in other words, there would be only slight damping of a transmitted pulse wave, in which case the "compensatory elevation" required would be slight. But, on the other hand, the thicker and more rigid the tube and the smaller its calibre, the greater would be the necessary compensatory elevation.

Also, (2) when the inside pulsatory oscillations are small the "compensatory elevation" is slight, but the greater the inside oscillations the greater must be the "compensatory elevation" of outside pressure.

And (3) if the calibre of the outside manometer is small, only a slight change in volume is required to fill up the space displaced in the proximal limb of the mercury which is depressed by the increase in pressure. Therefore, the arterial tube need not fluctuate greatly in volume in order to transmit the required pressure wave. In this case, the "compensatory elevation" of outside pressure would be relatively small. But when the outside manometer is large in calibre it will require large volume fluctuation of the arterial tube. This in turn will necessitate a large compensatory elevation.

So the favorable point above and below which the oscillations swing is not a definitely fixed point, but varies with the conditions of the experiment. However, *it is always necessary to have the mean outside pressure more or less elevated above the mean inside pressure.*

There is here, as in the diaphragm experiment described above, a "most favorable point" at which oscillations can be transmitted with the least damping. But it is unlike the diaphragm experiment in this regard: In the diaphragm experiment this most favorable level is a fixed point which never alters with altered amplitude of arterial pulsations, nor with thickness of the rubber diaphragm, nor with the calibre of the mercury manometer; whereas with the rubber tube experiment, this most favorable point is a movable point. That is, the point changes with the amplitude of arterial pulsations, with the ratio of the volume of the rubber tube to the calibre of the manometer. The reason for this difference between the location of the favorable point in the diaphragm and in the elastic tube is found in the volume-pressure

curves of these two mechanisms. The diaphragm transmits inside oscillations with least damping when the *mean* inside pressure is just equal to the *mean* outside pressure, for in this state the diaphragm is most completely relaxed and can fluctuate most freely inward or outward by bending and without much stretching. The essential point is that *the volume-pressure curves above and below this point are identical.* That is, the increased damping is equally increased whether the inside pulsation is negative or positive, or in other words whether it extends above or below this point. Therefore, no matter how great the inside pulsation, it must swing equally above and below this favorable point in order to suffer the least amount of damping. So also it is with the factor of calibre of the manometer. The greater the calibre of the manometer the greater must be the volume displaced by the movement of the column of mercury in a given change of pressure recorded by the manometer. Therefore, the greater the manometer's calibre the greater will be the amount of fluctuation of the diaphragm to displace the required amount of mercury. This means that the greater the calibre of the manometer the greater the damping effect caused by the stretching of the membrane. Nevertheless this greater damping effect would be exercised equally and identically above and below the most favorable point. Therefore, changes in the calibre of the manometer do not change the position of this most favorable point for transmitting oscillations.

Consider now, the same factors in the elastic tube experiment. With the elastic tube it was found that the most favorable level is not a fixed point, but varied with the conditions of the experiment. It varied with the amplitude of the arterial pulsations, with the calibre of the manometer, and with the calibre of the tube, and with the stiffness of the tube. The essential point here is that the volume-pressure curve is *not identical* above and below the point where the mean arterial pressure is just equal to the mean transmitted pressure, nor is it identical above and below any other point. But as seen above, the three phases of elasticity of the rubber tube included in this study are all different from one another. Therefore, the most favorable area on this curve for the transmission of any given inside oscillation will vary according to the amount of fluctuation of the tube which is caused by the oscillation. If the amount of fluctuation is extremely small the area is more toward the top of the second phase (fig. 9). As the arterial pulsations increase in magnitude, requiring greater fluctuation of the tube, the favorable region on the curve includes that part of the curve

which was used for the small pulsation, but there is added to it a lesser part from above and a greater part from below, when there is included all of the region in the upper and middle portion of the second phase. As arterial pulsations continue to increase in magnitude, the whole of the second phase is included together with a small portion of the third phase. After this, continued increase in magnitude of pulsations causes the addition of larger amounts of the third phase, with lesser amount of the second phase.

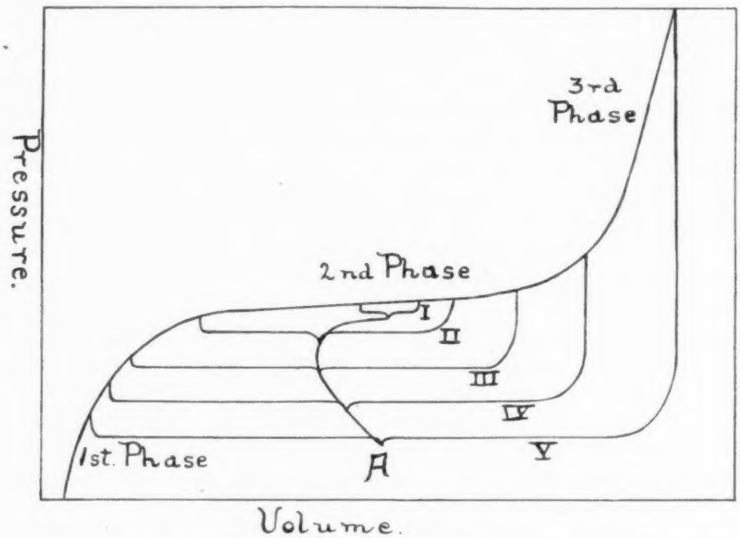

Fig. 9. I, II, III, IV, V, area of volume-pressure curve occupied by maximal transmitted oscillations when arterial oscillations are of different magnitude. I, minute arterial oscillation; *V*, large arterial oscillation; *A*, Alteration of mean point on maximal transmitted oscillation.

Thus, with very minute arterial pulsations, the *mean point* of the maximal transmitted oscillation is at the point where the outside pressure is at a level above the point where *mean* arterial is just equal to *mean* transmitted oscillation. As arterial oscillations are increased in amplitude, the *mean point* of transmitted oscillations moves upward. That is, the outside pressure must be increased in order to obtain maximal oscillations. This upward movement of the mean of outside maximal pulsation continues until the arterial pulse has increased to

such amplitude that the vessel is carried through the whole of the second phase and the lower portion of the third phase of the volume-pressure curve of the arterial tube. After this, further increase in amplitude of arterial pulsation causes the mean point of maximal outside pulsation to move downward again, for the third phase of the elastic tube transmits more favorably than does the first phase, and the increased fluctuations of the tube are made more in the third phase, and less in the first phase.

Or, in other words, as the arterial pulse wave increases from the very small pulse, on up to a large pulse wave, at first the mean outside pressure must be raised sufficiently above the mean inside pressure to just partially collapse the vessel. In this state the least amount of bending of its walls will give the required fluctuation in volume. This is the most favorable point for transmission of these minute oscillations. As the arterial pulsations are increased in amplitude, the mean outside pressure must be raised higher than it was with the small arterial pulsations, because the vessel is more easily bent inward or collapsed than it is bent outward or expanded, as is shown by the volume-pressure curve in this region. That is, when sufficient extra outside pressure is made the tube partially collapses because the outside pressure overcomes the natural tendency of the tube to assume a rounded shape. In this partially collapsed state the outside pressure balances the elasticity outward pull of the vessel toward the rounded shape. Here it is easier to swing the walls inward and further collapse the tube than it is to swing them outward and further dilate the tube. Therefore, as the arterial pulsations are increased in amplitude from the small oscillations up to somewhat larger ones, the outside pressure must be raised in order to secure maximal transmitted oscillations, for in so doing the advantage is taken of using more of the second phase where the fluctuation is easier, and using less of the upper and part of the second phase where fluctuation is more difficult (fig. 9). As the arterial pulsations are further increased, the mean outside pressure must continue to be raised still further in order to continue to make use of a greater added portion of the easy inward bend of the collapsing tube, and of a lesser added portion of the difficult fluctuation of the outward expanding tube.

This process continues until at the diastolic arterial pressure the vessel is so far collapsed that its walls are touching in the middle (fig. 8, *B*), or it has reached the top of the first phase of the volume-pressure curve where oscillations are transmitted with more difficulty than they are in the third phase (figs. 5, 9).

Therefore, from now on, as the arterial pulsations are further augmented it is easier to provide the increased fluctuation of the volume of the arterial tube by extra expansion with extra stretching of the walls during systole, than by extra compression with extra flattening of the already almost completely collapsed vessel. This requires that the mean of maximal transmitted oscillation shall turn about and instead of moving upward shall move downward, or shall not move upward, or at least shall not move upward as fast as before, i.e., upward or downward as regards the height of the cuff or outside pressure. So much for the effect of alterations in amplitude of arterial pulse on the location of the mean point of maximal transmitted oscillations. A similar discussion could be carried through either as regards calibre of manometer; resistance of vessel; or calibre of vessel. However, since the philosophy is very much the same in all these factors, it is deemed unnecessary to go through it here.

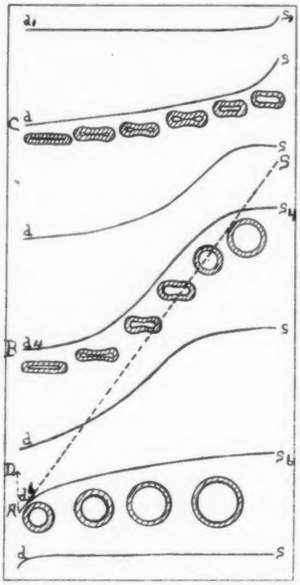

Fig. 10. Diagram showing curve of arterial or inside pressure from diastolic up to systolic and the resulting transmitted pressure curves produced when arm band or outside pressure is placed at various levels, together with the accompanying changes in the shape of the vessel. *D–S*, diastolic to systolic—true pressure; *d–s*, curves of transmitted oscillations from diastolic to systolic pressures, when outside pressure is placed at various levels.

Further light is cast upon the essential points of the whole problem by tracing with the above described apparatus on a moving drum, curves showing, not only the amplitude of the inside and outside pressure changes, but the form of the curves made by such a tracing. In short, while the drum was moving at a constant speed the inside pressure was raised from the diastolic point to the systolic point at a constant speed. This caused the inside pressure manometer to trace a straight line which was directed upward and to the right at an angle of about forty-five degrees with the base line (fig. 10, *D*, *S*.) Then the inside pressure bottle was lowered, at the same constant speed, back to diastolic level. These tracings were several

times repeated, the inside manometer traveling over the same line, but starting with the outside pressure at different levels.

It is noted that when beginning with the outside pressure high (fig. 10, d_1, s_1), there is very little change in the height of the outside pressure which was almost a straight line. When beginning with the outside pressure somewhat lower, there is very little change in the outside pressure curve, as the inside pressure rises from the diastolic up to the systolic level, until at the very last just before reaching systolic, when there is a sharp upward hook to the curve. It is also noted here that the arterial tube is rather tightly collapsed until the point where this sharp upward hook occurs, and there the tube begins to open slightly. Beginning with the outside pressure set at lower levels, the outside pressure curve alters as shown in the tracing and diagram in figure 10, d_4, s_4. Here where the point of greatest transmitted oscillations is reached it is noted that, beginning at the diastolic point, the outside pressure curve is at first slow in rising; then it rises sharply, and then more slowly again. It traces an S-shaped three phase curve, which is similar to the volume-pressure curve of the rubber tube. Also, it is noted that the arterial tube is more or less completely flattened at the beginning where the curve is slow in rising, then the tube opens out and becomes round in the region where the abrupt rise in pressure is noted, and the tube is partly distended in the upper region where the curve is again slowed down.

When beginning with the outside pressure low, say with inside and outside pressure equalized at the diastolic point (the point where according to Marey the greatest transmitted oscillations ought to occur (fig. 10, d_6, s_6) the transmitted oscillations are small. At first the arterial tube is passively rounded and the curve starts upward, but as the inside pressure continues to rise the arterial tube becomes partly distended at which point the curve sharply bends over and does not rise much afterward, while the inside pressure is continuing on its way up to systolic level.

These experiments are identical with those just described above except they show a graphic curve of the whole course and shape of the pressure curves on a moving drum, instead of merely showing their amplitude on a stationary drum. They show that the most favorable region for the transmission of pressure oscillations is when the arterial tube's walls are partially collapsed and can therefore fluctuate inward and outward, changing the volume easily, without involving any actual stretching of the walls. This required that the mean outside pressure must be higher than the mean inside pressure.

With these principles in mind a series of animal experiments was performed, as was mentioned in the introduction. The object of these animal experiments was to find out where the first oscillations occur and also where the greatest oscillations occur when an arm band was placed about a dog's neck, instead of a patient's arm, and when the pressure in the cuff was raised to a high point and then gradually lowered. The arrangement is shown in figure 11. But in order to

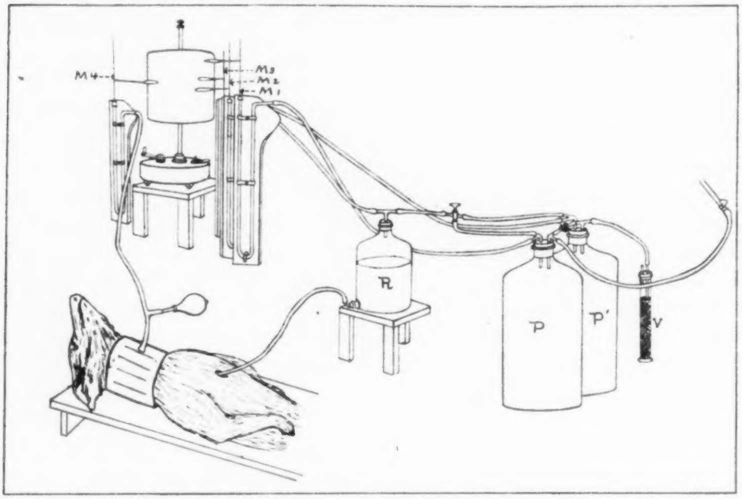

Fig. 11. Arrangement of apparatus for producing artificial pulsatory oscillations of pressure in dog's aorta and for recording the oscillations transmitted by an arm band placed about the dog's neck. *P*, systolic pressure; *P'*, diastolic pressure; *R*, reservoir of defibrinated blood; *M1*, systolic pressure manometer; *M2*, diastolic pressure manometer; *M3*, manometer recording artificial pulsatory oscillations; *M4*, manometer recording arm band pressure transmitted oscillations; *V*, mercury valve.

attain this object, an artificial heart beat was substituted for the dog's own heart beat. The purpose of this was to have a known diastolic and systolic pressure in the aorta and great vessels and to make the pulse beats slow enough to permit the mercury manometer to register accurately. For, when experiments in this field are attempted using the dog's own heart beat, the actual pressure curve in the aorta is not known. Maximal and minimal valves do not remedy this difficulty for they select and record only the highest and lowest beats and there-

by they do not measure the general course of the average diastolic nor that of the average systolic pressure and furthermore they are not accurate, whereas the oscillations of the manometer that are used to measure the diastolic and the systolic pressures are not oscillations produced only by the highest and lowest beats but they are produced by a series of uniform beats. Furthermore, if the rate of the heart beat coincides with the period of the manometer the oscillations are greatly augmented, but when the rate of pulse beat is such that it clashes with the period of the manometer the oscillations of the manometer are greatly diminished. So that a given pulsatory pressure, when its rhythm is coincident with the period of the manometer, may cause oscillations of the manometer which are several times greater than the same pulsatory pressure at a rhythm which interferes or does not coincide with the period of the manometer.

Therefore, to eliminate the unknown and variable quantity of the dog's own heart beat, an artificial pulse beat was used; and to eliminate the error of augmentation of oscillation of the manometer caused by coincidence or the error of diminution of oscillations caused by interference of rhythm with the period of the manometer, the artificial pulsations were made so slowly that neither interference not coincidence could occur.

The dog was anesthetized with ether and a snugly fitting cannula was inserted into the abdominal aorta close under the diaphragm. By a large rubber tube the cannula was connected with a large three-way cock which led to two large reservoir bottles one on each side, containing blood mixed with 0.9 per cent NaCl. One of these bottles was kept at high pressure (systolic), and the other at a low pressure (diastolic). Each bottle had connected with it a manometer which traced on the drum throughout the experiment. The heads of pressure in these two bottles were kept constant, as was shown by their respective manometers, by having the high pressure or systolic bottle freely connected with the air pressure system of the laboratory, which is a forty gallon tank with a safety valve and the pressure supplied by an air pump run by an electric motor. While the experiment was in progress the safety valve was set at the desired (systolic) pressure and the pump was kept going so that some air was constantly blowing off. This maintained the systolic pressure bottle at a constant. Leading from the air pressure system was another connection which led to the low (diastolic) pressure bottle; but this was a narrow connection. That is, the rubber tube was almost closed by a screw clip, so that a small stream

of air from the air pressure system was constantly blowing through the narrow slit into the low pressure reservoir. In order to hold the pressure in this bottle at the desired (diastolic) level, a mercury valve (or a glass tube dipping under mercury) was connected with the bottle. So by adjusting the depth of the tube under the mercury the pressure of the air in the bottle could be controlled. When the valve was so adjusted and the pressures had become equalized there was always a small stream of air bubbling through the mercury valve.

When all was ready the dog's trachea was opened and a long metal tracheal cannula inserted far down the trachea, or else if a short cannula was used the trachea was dissected out and turned upward. Then an arm band was placed about the dog's neck which had been shaved. The arm band included the cannula if it could be done without shutting off the dog's respirations; if not, the trachea and tracheal cannula were not included within the arm band. The arm band pressure was traced by a manometer on a drum. Now the dog's heart was stopped by crowding the anesthetic. Next the artificial arterial pulsations were made by turning the three-way cock now right now left, connecting the aorta first with the systolic then with the diastolic pressure bottles.

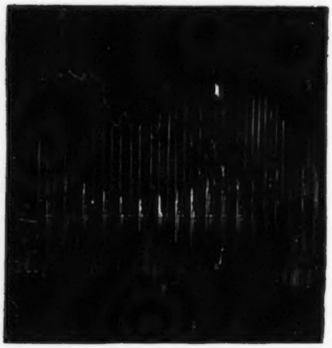

Fig. 12. Blood pressure tracing, arm band around dog's neck, cannula in abdominal aorta, arterial pulsations of pressure made artificially.

The cuff pressure was raised to a high point and allowed to fall gradually. The tracings showed a great similarity to those described above on the artificial model. The main points to be noted are similar to those noted above on the experiments on the model. The first oscillations begin at a point above the true maximal or systolic pressure, the height being directly proportional to the delicacy of the technique. The greatest oscillations on the tracing are at a point above the true diastolic pressure (fig. 12).

In most of our experiments this error is 1 or 2 cm. Since the animals were normal and their blood vessels therefore soft and not sclerotic and since they were deeply under the anesthetic, this small error ought not to be surprising. If we had encountered a rigid pair of carotids we doubtless would have found a much greater error.

As regards the mechanism of the production of the sounds which are used for criteria in measuring blood pressure by auscultation, the work of MacWilliam and Melvin (7) is for the most part correct. However, we have approached the problem somewhat differently, and have some additional observations to report.

An artificial model was prepared with a soft piece of rubber tubing of suitable length placed inside a glass tube and connected by a three-way cock with a high or systolic pressure bottle, and also with a low

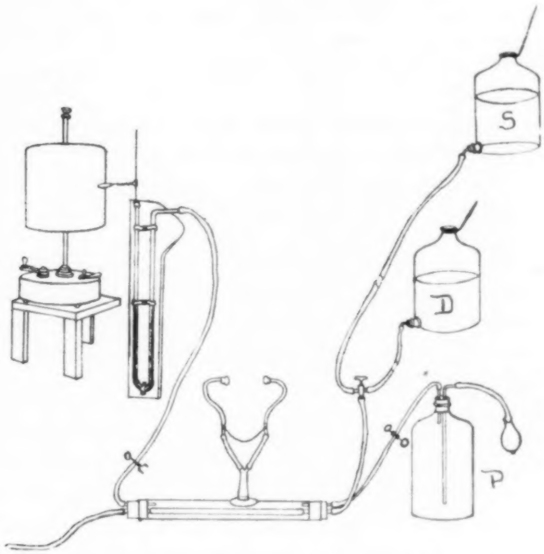

Fig. 13. Arrangement for studying the mechanism of the production of sounds used in auditory blood pressure method.

or diastolic pressure bottle. The bottles were placed at the desired levels. Pulsations were made inside the rubber tube by turning the glass three-way cock first on the systolic and then on the diastolic pressure bottle. The piece of rubber tube connected through short brass tubes through rubber corks to the sources of pressure on one end and to a short soft piece of rubber tubing on the other end (fig. 13). Through another brass tube inserted through the rubber cork, air pressure was made in the space outside the rubber tube and within the large glass tube. This outside space, through a T-tube communicated with the

mercury manometer. Also in some experiments, a venous return rubber tube was brought back through the outside air space of the large glass tube and in some no peripheral tube at all was used. A stethoscope was sealed on to the side of the glass tube with wax or paste. When this was done, sounds were produced which roughly correspond with those produced in the artery which is compressed by the arm band during the determination of blood pressure by the auditory method.

The results were as follows:

The first sharp sound (first phase) which is heard when the arm band pressure is gradually lowered, occurs when the elastic vessel or tube is tightly closed except at the top of systole at which point a small spurt of fluid escapes through the narrow slit between the sides of the collapsed vessel.

The first dull sound (second phase) which is heard when the arm band or outside pressure is still further lowered, occurs when it is quickly opened and closed at each pulse beat.

The second sharp sound (third phase) occurs when the vessel is open except at the bottom of diastole, at which point the vessel closes for an instant and in doing so reduces the column of fluid to a small jet which passes through the narrow silt between the collapsed vessel walls.

The second short dull sound (fourth phase) occurs when the vessel is at no time completely closed, not even at diastole, but the vessel is partly collapsed at diastole and fairly well, but not completely distended at systole.

These facts regarding the relation of the vessel to the production of the sounds are presented without at present trying to account decisively for all the various other conditions which are associated with the production of these sounds.

However, it would seem that the nozzle-swish of the fluid through the narrow orifice may well be the chief factor in the production of this sharp sound of the first and third phases.

Also, for the second phase, the sudden opening and closing of the vessel together with the sudden joining and separation of the column of liquid may well be the chief factors in the production of these sounds.

In the fourth phase the stretching and partial collapsing of the vessel, together with its disturbing effects on the flow of liquid may well be the factors concerned in the mechanism of the production of these sounds.

The relation and importance of these and other various conditions we hope to study in the future.

SUMMARY AND CONCLUSIONS

The commonly accepted criteria for obtaining the systolic and diastolic blood pressures do not yield correct results, but give readings which are too high. The amount of error depends upon and varies directly as the resistance of the vessels to compression and expansion.

That is, the true systolic pressure is somewhat lower than the point where the arm band pressure is just sufficient to cut off the radial pulse, and it is also lower than the point where a manometer, connected with the arm band pressure, when the arm band pressure is gradually lowered from a high point, shows the beginning of oscillations. The height at which these beginning oscillations first appear depends upon the delicacy of the recording mechanism. The true systolic pressure may also be lower than the various points in the tracing of arm band pressure where there are certain alterations in the form of the tracing; a dicrotic notch, widening of the limbs, a sudden increase of augmentation. The exact significance of these latter criteria is not yet known.

That is, secondly, the true diastolic pressure is somewhere lower than the lowest point of the greatest oscillations that are produced by the manometer connected with the arm band pressure, when the arm band pressure is varied until the point of greatest oscillations is located.

This is contrary to Marey's principle.

In order to employ these criteria to measure blood pressure a correction is necessary. Unfortunately the amount of correction varies with the resistance of the arteries to compression and expansion. In soft arteries the error is not large, but in arteries made resistant by disease or by contraction of their muscular elements, it must be very great.

This same error is inherent in the auditory as well as the graphic method of measuring blood pressure.

The sharp sounds of the first and third phases of the auditory method of measuring blood pressure occur when the blood is passing through a narrow slit between the almost completely collapsed vessel. Therefore, the sounds may be due to a nozzle-swish action.

The first dull sound heard in the second phase occurs when the vessel opens and closes quickly. Therefore, the sounds may be due to the stretching of the walls, the sudden closure of the vessel, or the alteration in the flow of blood through the vessel, sudden separation and joining of the column of blood.

The second dull sound heard in the fourth phase occurs when the vessel, even during diastole, is not completely closed, but it is partly collapsed in diastole and partly distended during systole. Therefore, the sound may be due to the partial collapsing and the partial distention of the vessel together with the disturbing effects of this on the blood flow through the vessel.

BIBLIOGRAPHY

(1) Marey: Trav. d. Laboratoire, 1876, ii, 316; also Marey: Ibid. 1880, iv, 253.
(2) Martin: Brit. Med. Journ., 1905, i, 865.
(3) Mosso: Arch. Ital. d. Biol., 1805, xxiii, 177.
(4) Roy and Adami: Practitioner, 1890, xlv, 32.
(5) Hill and Bernard: Lancet, 1898, i, 282.
(6) Oliver: Studies in blood pressure, 1904, 2nd ed.; also Oliver: Quar. Journ. Exp. Physiol., 1911, iv, 45.
(7) MacWilliam and Melvin: Heart, v, 153.
(8) Wiggers: Circulation in health and disease, 1915, 210.
(9) Christen: Dynamische Pulsuntersuchungen, Leipzig, 1914.

SUPPLEMENTARY NOTE

We are surprised to find just as we go to press that Joseph Erlanger has adopted the main idea of our work which we presented and demonstrated in his laboratory at the December, 1914, meeting of the American Physiological Society, and has published it in this Journal in the number just prior to the present number. We are pleased thus to have a good portion of our work confirmed just before its appearance in the Journal, but we regret that our long deliberation has resulted in the confirming paper appearing just before the original contribution.

STUDIES ON ABSORPTION FROM SEROUS CAVITIES

I. The Omentum as a Factor in Absorption from the Peritoneal Cavity

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The studies which have been made from time to time on the mechanism of absorption of granules from the peritoneal cavity and the pathways over which such absorption takes place have all tended to emphasize the importance of the diaphragm as the active agent in this process, and have indicated the diaphragmatic lymphatics as the channels through which granular material of all sorts passes to reach the lymph glands and other organs in which it is eventually found. Although pathologists and clinicians have long been aware of the activity of the omentum in peritonitides of various sorts, the possibility of an absorptive function on the part of the omentum has been either discredited or disregarded. Indeed there is noticeable a decided disposition on the part of the various investigators who have studied the problems which the drainage of the peritoneal cavity presents, to evade discussing the question of the omentum's share in ridding the peritoneal cavity of foreign substances, a disposition which is excusable in the light of the difficulties which obtaining a definite answer to the question presents. For example MacCallum (1) ignores the omentum entirely. Buxton and Torrey (2), discussing the possibility of an exodus of granular material from the peritoneal cavity by other channels than the diaphragmatic lymphatics speak of absorption via the omentum in the following words:

> The omentum appears to furnish such an additional channel to some extent. Sections made from the omentum within an hour after injection of lamp black into the peritoneal cavity show that the afferent plexuses of the lymph nodes are filled with free particles. After two or three hours the particles have been taken up by the macrophages and lie principally in the sinuses of the node.
>
> All this corresponds precisely with processes seen in the anterior mediastinal lymph nodes, so without going into further details we may take it as probable

that the lymphatics of the omentum, as well as those of the diaphragm, are concerned in the initial rapid rush of particles to the organs, though probably to a less extent.

They believe that the mass of the foreign material which can be found in the rolled up omentum after the induction of a foreign body peritonitis is merely adherent to or buried in the tissue of that organ.

Those authors who admit the possibilities of the omentum as an absorptive pathway are unanimous in the belief that absorption of granules takes place via the omental lymphatics. In the absence of definite knowledge of the facts of the case such a conclusion as regards the absorption of particulate matter is logical when we consider the part which lymphatic radicles play in the removal of granules from any locality, and the ease with which granular material injected into the peritoneal cavity may be recovered from the lymphatic glands. However, it is by no means certain that there are any lymphatics in the omentum at all. Ranvier (3) has shown that while lymphatic vessels may be found in new born kittens they are obliterated and disappear before the animal has reached adult age. If they are present they are certainly not numerous or easy to demonstrate, the silver technique which brings out their outline so beautifully in the diaphragm and other regions failing to show them in this situation.

The absorption of true solutions from the peritoneal cavity has been the subject of extensive researches, which have for their object the establishment of the blood stream or the lymphatic channels as the pathway by which fluids leave the peritoneum. Melzer and Adler (4) have studied these absorption routes by injecting solutions of strychnine and potassium ferrocyanide into the peritonea of normal animals in which the entrance of lymph into the blood stream had been prevented by previous ligation of both innominate veins. They found that strychnine convulsions and the appearance of the Prussian blue reaction in the urine were much delayed in animals whose innominate veins had been tied previous to intraperitoneal injection and they, with Muscatello (5), are the chief advocates of lymphatic absorption. Haidenhain (6), Cohnstein (7), Hamburger (8), Starling and Tubby (9), and others have advanced good evidence of absorption via the blood stream and lately Dandy and Rowntree (10) have shown that, after intraperitoneal injection of phenolsulphonphthalein the dye rapidly appears in the blood and in the urine while lymph from the thoracic duct contains little or none of the dye. They draw the very logical conclusion that the haemic route is the important one for the

absorption of fluids and that the importance of the lymphatic vessels in this function has been vastly overestimated.

If a peritonitis is induced by injecting suspensions of a granular foreign body into the peritoneal cavity large phagocytic cells may be recovered from the blood of the portal vein which contain in their cytoplasm phagocytized granules of the intraperitoneally injected material. That these are none other than the "pyrrhol cells" or "makrophages" which have been described in animals stained vitally with vital azo dyes is at once evident on examining the portal blood of a trypan blue stained animal after the induction of a foreign body peritonitis with cinnibar or filtered India ink. Smears from the portal vein blood of such an animal show numbers of pyrrhol cells in whose cytoplasm cinnibar or India ink granules may be seen sharply contrasted with the segregated masses of the blue dye.

The presence of such cells in the portal vein is sufficient to direct attention to the possibility of the removal of foreign particles from the peritoneum through the omental blood vessels. The connective tissues of the omentum which fill the meshes of its vascular network are very rich in these wandering phagocytes and there are large masses of them, the so called "taiches laiteuse," in close association with capillary knots or glomeruli. Because of this close association it is not difficult to imagine pyrrhol cells laden with foreign material as penetrating the walls of some of the omental veins and being carried into the portal circulation into which those veins drain.

By far the most remarkable feature noticeable about the portal blood, however, is the presence in it of large quantities of ink or cinnibar which are not enclosed in cell cytoplasm, but which are perfectly free in the blood plasma. Most of this foreign material is in the form of fine granules, but in some cases the ink or cinnibar may be seen in masses which represent aggregates of the finely divided particulate matter in suspension.

Sections of the livers of these animals show pictures which differ according to the length of time which elapsed between the injection of the foreign body into the animal and its execution. The livers of animals killed a short time after the injection are apparently normal, save that the phagocytic endothelium contains varying amounts of foreign pigment which has come from the peritoneal cavity. The portal vein and the hepatic capillaries contain numbers of phagocytes, which have in their cytoplasm, besides the vital dye with which they were previously colored, the granular material which they have engulfed

from the intraperitoneally injected suspension. These vessels also contain numbers of granules and aggregates of cinnibar or India ink.

If the animals have been allowed to live 24 hours or more after the injection of cinnibar, the liver shows constant abnormalities. That there is still an influx of granular material coming from the peritoneum is evident from the presence of fine granular material and macrophages in the portal veins and the capillaries. The liver is studded throughout with numerous foreign body giant cells of huge size, some of them having fifty or more nuclei whose cytoplasm is stuffed full of phagocytized cinnibar and vitally stained with trypan blue. The portal veins are dilated and full of blood almost to bursting, as though we had to deal with a partial blocking and a passive congestion. On the other hand, the intralobular veins are found dilated or empty, save for a few red blood cells and leucocytes, among the latter being some free pyrrhol cells usually with cinnibar inclusions. We cannot at this time discuss the origin of these giant cells. Whether they are all formed from the phagocytic liver endothelium, or whether immigrated macrophages which have been caught in the liver capillaries have any part in their formation, we cannot say at present.

While these findings are suggestive of the absorption of granular materials by way of the blood stream and point to the omentum as the organ where this absorption takes place, they cannot be accepted as proof of fact, since there is no way of excluding the diaphragmatic lymphatics from participation in the removal of substances from the peritoneum and the entrance of granular material into the circulation via the thoracic duct. For these reasons it was necessary, in order to establish absorption by the omentum beyond question, to bring that organ into contact with solutions and suspensions in such a way that foreign material could not find its way to other absorbing surfaces. This was accomplished by drawing the omentum out of the body of the animal through a midline incision and immersing it in the fluid which we wished to study. Participation of the lymphatics in the absorption of the material was eliminated by preliminary ligation of the thoracic duct. Since these experiments must of necessity run for several hours in many cases, the difficulties of the anaesthesia problem are obvious and we finally came to use animals upon which the operation of decerebration had been performed. Decerebrate animals are ideal material for such experimentation since they lie motionless and rigid with regular pulse and respiration, and blood pressure which is more nearly normal than that of any anaesthetized animal. The omenta of animals pre-

pared in the manner described above were immersed in true solutions, in pseudo solutions of high molecular dyestuffs like trypan blue, in colloidal metals, and in filtered India ink. After exposure for varying lengths of time, the animals were killed and their tissues examined.

Up to the present time little has been known about the organs concerned in the removal of fluid from the peritoneal cavity and the previous deductions about the vascular path of removal have been based almost entirely upon pharmacological studies, e.g., the work of Melzer, and others with strychnine solutions and that of Dandy and Rowntree on the absorption of phenolsulphonphthalein. Except for the experiments of Rubin (11) on peritoneal absorption in animals whose omenta had been resected there is no experimental evidence which indicates the omentum as a fluid absorbing surface.

In these studies on the absorption of solutions by the isolated omentum we have for the first time attempted to use a histological method of attack in localizing the absorbing surfaces of the peritoneum by exposing the omentum to solutions of potassium ferro cyanide and iron ammonium citrate and fixing the omentum, liver, kidneys, lymph glands, etc., of the sacrificed animals in acid formalin. It was hoped that a study of the distribution of the resulting precipitates of Prussian blue would throw some light on the route of removal of the original fluid and the mechanism by which it found its way into the channel of escape. The citrate ferro cyanide solutions were exactly isotonic with the blood plasma so that any interference by a difference in osmotic pressure was negligible. It may be well to emphasize here the fact that the pressure on the omentum and the fluid to be absorbed—the intra-abdominal pressure—was lowered by exposure of the omentum to the air. This is far from being the case when studies on absorption are made by injecting fluids intraperitoneally. Even small amounts of fluid have a tendency to raise the intra-abdominal pressure and the tremendous rise in pressure which must follow injections of the large volumes of fluid used by some workers cannot but materially affect the mechanism of absorption and drainage.

True solutions and pseudo solutions are absorbed through the blood vessels of the omentum very rapidly. The kidneys of animals killed three hours after immersion of the omentum in the citrate-cyanide solution and fixed in acid formalin show macroscopically on section a deep blue color in the papillae and the cortex due to precipitation of the Prussian blue by the acid. Masses of Prussian blue are visible on section about the portal vessels in the liver. Spread preparations of

the omentum and microscopic sections show the omental veins to be filled with Prussian blue precipitated in granules so fine as to have the appearance of an homogeneous mass when examined with the highest power dry lenses. Finely divided precipitates of Prussian blue can be seen in the cytoplasm of the endothelial cells themselves though the cell nuclei are always free from any granular deposit.

Since Melzer suggests that ligation of the large lymphatic ducts may cause a stasis followed by an increased pressure on the fluid in the tissue spaces and a consequent abnormal flow of that fluid into the blood vessels, these experiments were repeated on animals without ligation of the thoracic duct. The results were identical.

Experiments with trypan blue were especially striking; an hour's exposure of the omentum to a 1 per cent solution of the dye resulted in a very perceptible staining of the animal's skin and mucous membrane.

Granules of particulate material are absorbed along the same channels, since after exposure of the omentum to filtered India ink, carbon granules may be found in the portal veins. The granules absorbed are very small and where masses of ink were found they were evidently aggregates of very fine particles. The aggregates seem most liable to occur if the circulation is for any reason poor or impeded.

The drainage of particulate matter from the serous cavities via the blood stream is most extraordinary and was most unexpected since the blood vessel wall is not credited with permitting the passage of anything but fluids with a possible exception in the capillaries of the intestinal mucosa. It is probable that only the very small granules of ink pass into the omental veins and we hope soon to be able to state more definitely the granular size limits within which this is possible. Microscopic sections of the livers of these animals show that some ink is phagocytized by the capillary endothelium but most is found as free granules in the lumen of blood vessels. In all a considerable amount of granular material must leave the cavity of the peritoneum through omental veins.

In none of our sections or the numerous span preparations which we have made by various methods have we been able to find lymphatic vessels in the omentum in any of our animals and our sections show clearly that even if such vessels exist, omental lymphatics have no important rôle in the drainage of the peritoneal cavity. On the other hand the omentum plays a very large part in the actual drainage of the peritoneal cavity. True and pseudo solutions and granules of particulate material find their way through omental vessels to the organs

of the body destined for their ultimate reception and storage or destruction and excretion, and the path by which they leave the omentum is not a lymphatic but a haemic one.

In a later communication we shall describe fully the manner in which various substances pass through the blood vascular and lymphatic walls and their fate after their entrance into the blood and lymphatic circulation. Studies are now under way on the exit of true solutions, colloids and particulate substances through the various absorbing surfaces of the serous cavities of the body.

BIBLIOGRAPHY

(1) MacCallum, W. G.: Johns Hopkins Hospital Bull., 1903, xiv, 105.
(2) Buxton, B. H. and Torrey, J. C.: Journ. Med. Research, 1906, xv, 5.
(3) Ranvier, L.: C. R. Ac. des sc., 1896, cxxii, 578.
(4) Adler, I. and Meltzer, S. J.: Journ. Exper. Med., 1896, i, 482.
(5) Muscatello, G.: Arch. f. Path. Anat., 1895, cxlii, 327.
(6) Heidenhain, R.: Pflüger's Arch. f. d. gesammt. Physiol., 1891, xlix, 209.
(7) Cohnstein, W.: Zentralbl. f. Physiol., 1895, ix, 401.
(8) Hamburger, H. J.: Zentralbl. f. Physiol., 1895, ix, 484.
(9) Starling, E. H. and Tubby, O. H.: Journ. of Physiol., 1894, xvi, 140.
(10) Dandy, W. E. and Rowntree, L. G.: Annals of Surgery, 1914, lix, 587.
(11) Rubin, I. C.: Surgery, Gynecology and Obstetrics, 1911, xii, 117.

STUDIES IN BLOOD PRESSURE ESTIMATION BY INDIRECT METHODS

II. The Mechanism of the Compression Sounds of Korotkoff[1]

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The preceding paper of this series (1) concerned itself with the mechanism of the oscillatory method of determining the blood pressure. In the course of that study parallel observations were made on the sounds that can be heard in the artery below the local compression in the hope that information might thus be gained with regard to the origin of the compression sounds of Korotkoff. The outcome was a working hypothesis. In the present paper this hypothesis is elaborated and the experiments devised for the purpose of testing its validity, as well as that of recorded hypotheses, are presented.

SUMMARY OF VIEWS ON THE MECHANISM OF THE KOROTKOFF SOUNDS

In reviewing the views held with regard to the causation of the compression sounds of Korotkoff, it might be well first to call to mind the mechanism of the production of sounds in general and of arterial sounds in particular. Physics teaches that sounds arise from vibrating sources. If the vibrations are regular and of sufficient frequency a musical note is heard. The pitch of a sound is determined by the frequency of the vibrations, its loudness by the amplitude of the vibrations. The frequency of a vibrating membrane or arterial wall bears an inverse relation to the area of the membrane participating and a direct relation to its tension; while the amplitude of the vibrations depends upon the blow struck, which is determined by the magnitude and rate of development of the pressure or tension that starts the vibrations. We owe primarily to Friedreich (2) the demonstration of the fact that arterial

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sounds partaking of the quality of notes are due to sudden changes, either an increase or a decrease, in the tension of the arterial wall, and that murmurs are determined by eddies set up beyond a constriction in the bed of the stream.

The views held with regard to the origin of the compression sounds of Korotkoff, now extensively employed in the estimation of the arterial blood pressures in man, may, for the sake of convenience, be divided into two groups:

a. Views locating the production of sound in an empty artery beyond the compression. Korotkoff is apparently of the view that compression sounds are due to "the forcing apart of the wall (of the artery) by the first stream of blood which reaches the artery below the cuff. He maintains that the lower part of the brachial artery, during the time the compression is exerted above it, is in a condition of complete relaxation and that the first blood stream causes a sudden sharp stretching of the wall with the consequent production of sounds." Korotkoff offers as proof of this contention the fact that a sound is produced when salt solution is poured into the iliac artery of an animal (3). This view or slight modifications of it (4) seem to be held by the majority of those who have devoted some thought to the subject.

b. Views locating the seat of sound production in the part of the artery compressed apparently are to be found only in the very recent literature. In 1914 MacWilliam and Melvin (5) were forced to this conclusion by the observation that the "sounds are perfectly well developed and characteristic" when the *artery* consists merely of a tube in a compression chamber. These investigators ascribe the sound to vibrations determined by a change in the form of the tube in the compression chamber. It might be added here that the changes in form they describe are not those that occur under a pulse of the configuration of the arterial pulse (1). Flack, Hill and McQueen (6), maintain, without however, offering any experimental evidence for their view, that the compressing armlet "converts the compressed area (of the arm) into a resonating mass, the pulse is not damped down in the labile arteries, but strikes the blood which fills to distention, not only the main artery, but every patent arteriole throughout the mass, and causes the whole tense mass to vibrate."

Von Frey's explanation of the fact that when the arm is plunged vertically into a dish of mercury the shock of the pulse can be felt with special distinctness at a very definite point, is of interest in this connection. He is of the opinion (7) that the pulse is felt most distinctly

at that place because there the blood flow is checked, the pulse waves are reflected positively, and the summation that results gives to the waves sufficient energy to produce a sensible pulsation. It may, however, be said now that this explanation cannot be the correct one, for if it were, the sensation caused by simply occluding the artery should be as intense as the sensation that is experienced when the compressing pressure lies between the systolic and diastolic level. As is well known, this is not the case.

Gittings (8), while accepting the view with regard to sound production prevailing at the time he writes (1910), believes that the compression chamber contributes to the sound by virtue of its action as a resonator. This conclusion he bases upon the observation that the sounds are much louder when the artery is compressed with the usual pneumatic cuff than with an Esmarch bandage.

THE NEW HYPOTHESIS

The investigation of arterial sounds which forms the basis of this paper forces us to the conclusion that the main mechanism of the compression sounds is as follows: Under compressions which permit the pulse to determine relatively wide excursions of the arterial wall in the compression chamber, that is, under compressing pressures ranging from systolic arterial pressure to, and even a variable distance below, diastolic pressure, the volume of the compressed artery increases abruptly with each pulse (1). This permits a considerable volume of blood to enter the opening artery with a high velocity. The motion of this column of blood is, however, suddenly checked where it comes into contact with the stationary, or practically stationary, column of blood filling the uncompressed artery below. The water hammer that is thus set into play distends the arterial wall at the point of impact with unusual violence. This distention sets the arterial wall into vibration and the sound is produced.

Water hammer may be defined as the pressure exerted when the motion of a mass of fluid is more or less suddenly checked. Some idea of the powerful effects of water hammer is gained from the statement (9) that the rise in pressure caused by suddenly stopping the flow of water in a pipe may be so great as to cause the bursting of the pipe. The following crude experiment, made under mechanical conditions that resemble somewhat those obtaining in blood pressure observations, will serve to indicate the magnitude of the forces we have to deal with in the present problem. A pressure bottle was connected with a

mercury manometer by rubber tubing of 7 mm. bore through a maximum valve. The whole was filled with water and the bottle was elevated until it exerted a pressure of 140 mm. of mercury on the manometer. The rubber tube was then compressed close to the valve by grasping it between the finger tips, held close together, and the ball of the thumb. This was done in such a way as not to alter the pressure indicated by the manometer. Then the compression was released as quickly as possible. The rate of decompression thus produced is probably somewhat faster than the rate of rise of pressure determined by the arterial pulse. With the decompression, the momentum of the water rushing to fill the tube as it opened drove the stationary mercury of the manometer 40 mm. above the level sustained by the head of pressure of the bottle. It is not without interest to add that at the same time a sound can be heard by listening over the tube with a phonendoscope.

The factors at work in developing the maximum pressure exerted by a water hammer are given by Joukowsky (10) in the following formula:

$$P = \frac{\lambda V w}{g} \qquad (1)$$

where

P = water hammer pressure (in excess of the static pressure),
λ = the velocity of wave motion,
V = the extinguished velocity of the fluid,
w = the weight of a cubic unit of the fluid, and,
g = the acceleration due to gravity.

If the conditions obtaining in blood pressure observations were as simple as those the hydraulic engineer has to deal with it would not be difficult to determine more or less accurately the values for the factors of Joukowsky's formula. The problem of the physiologist, however, is complicated by the fact that he has to do with a pulsatile instead of a steady progression of fluid through tubes which, instead of being rigid, though elastic, distend markedly under pressure and collapse under compression; that the flow is checked not by a rigid valve but by a column of stationary, or practically stationary, fluid contained in a tube of variable bore.

For the present we are interested only in those factors of the formula that would vary in the course of a blood pressure observation; they are λ and V. For present purposes therefore

$$P = \lambda V. \qquad (2)$$

From Tigerstedt (11) we obtain the following formula for λ:

$$\lambda = k\sqrt{\frac{g\,e\,a}{\Delta\,d}} \tag{3}$$

in which

g = the acceleration due to gravity,
e = the coefficient of elasticity,
a = the thickness of the wall of the tube,
Δ = the specific gravity of the fluid,
d = the bore of the tube, and,
k = a constant.

It is obvious that in a blood pressure experiment, practically the only variables of this formula would be the coefficient of elasticity, the bore of the artery and the thickness of the wall. Grünmach (12) has shown, in the case of artery, that the effect both of bore and thickness of wall is almost negligible relative to the effect of the coefficient of elasticity, and we actually know that both the coefficient of elasticity and the rate of transmission of the pulse increase with the distention of the artery. We may therefore conclude that during decompression of an artery the factor, λ, of formula *2* tends to increase.

It is much more difficult to derive the extinguished velocity, V. It will depend on the velocity the blood has attained in the compressed segment of artery at the moment of the impact with the column of blood below, and upon the degree the column of blood in the artery below checks this motion. It is practically impossible to obtain the absolute values of these factors. Discussing first the velocity at the time the blow is struck, it seems justifiable to assume that resistance to flow will cause a short though measurable time to elapse before the blood can traverse the length of the compressed segment of artery as it is opened by the rising pressure of the pulse. The velocity through the compressed segment would therefore tend to increase as, during decompression, the walls of the artery are more and more readily pressed apart. Another factor probably exerting an effect upon velocity is the difference between the compressing and the arterial pressures at the moment the blow is struck. If no time were required for the blood to traverse the length of the compressed segment it is obvious that there would never be any pressure difference. If, again, the time required to traverse the artery were brief and constant throughout decompression then, since the earlier parts of the anacrotic limb of the pulse wave rise more rapidly than the later parts, the force

driving the blood, and consequently the velocity of flow, would increase with decompression. But it is during the later phases of decompression that low resistance to the flow would tend to shorten the time required to strike the blow, and so diminish the effective difference between compressing and arterial pressures. We find, therefore, that what seem to be the two main factors influencing velocity so act during decompression as to oppose each other. Obviously it is difficult to reach a satisfactory conclusion with regard to the effect of lowering the compressing pressure upon the velocity of the initial flow in the compressed segment by a priori considerations alone.

To know the value of V in formula *2* it is still necessary to ascertain the degree to which the column of blood below checks the flow. It seems fair to conclude that the factors checking a moving column are essentially similar to those that affect the water hammer phenomenon in general; the forces acting to suddenly check a moving column are also the very ones that would oppose an effort to suddenly set a stationary column into motion. It would therefore seem that the suddenness with which the moving column is checked will vary mainly as the coefficiency of elasticity of the lower part of the artery. The checking effect will therefore increase as the lower artery distends. It may consequently be concluded that V of formula *2* increases during decompression.

Since both λ and V of formula *2* seemingly increase as the compressing pressure falls from the systolic to the diastolic level, we may conclude that water hammer action likewise increases.

Estimated velocity of flow in the dilating artery. The first paper of this series furnished data indicating the existence of conditions compatible with water hammer action during blood pressure observations. It was there shown that as long as the compressing pressure exceeds the diastolic pressure the artery is closed, or practically so, during a part of each pulse cycle. This means that the column of blood in the distal artery is stationary, or practically so, in the part of the cycle immediately preceding the arrival of the pulse. It was also shown that during the systolic-diastolic period of decompression a considerable volume of blood (as indicated by the volume of the compression pulse) descends with each pulse to fill the collapsed artery. If we assume that the artery fills just to its undistended bore with the particular systole that terminates the first rapid increase in pulse volume, as seen when the compressing pressure falls below the systolic level in records of the volume of the compression pulse [eighth pulse Table IV, fig. 18 (1)],

we may regard the volume increase per pulse at this time as the minimum quantity of blood that will, at all lower compressing pressures down to the diastolic level, enter the artery as it opens. On this basis it is possible to calculate the bore of the artery at this time and from the bore the velocity with which the first column of blood enters the artery. From information obtainable in figure 18 and Table IV of the preceding paper (1) it can be calculated that the systolic increase in volume with pulse no. 8 amounts in round numbers to 0.2 cc. and that the increase is practically completed in 0.09 second. The bore of the artery at this time is therefore $\left(\text{area} = \frac{\text{volume}}{\text{length}} = \frac{0.2 \text{ cc.}}{5 \text{ cm.}} = \right)$ 0.04 sq. cm. and the velocity of flow $\left(\text{velocity} = \frac{\text{volume}}{\text{area} \times \text{time}} = \frac{0.2 \text{ cc.}}{0.04 \text{ sq. cm.} \times 0.09 \text{ sec.}} = \right)$ 55 cm. per second. How rapidly this column of blood moves can best be realized by comparing it with the probable mean velocity of flow in the brachial artery of man. On the basis of data obtained from an article by Hewlett and Van Zwaluwenburg (13) we estimate that the former is at least twenty times the latter. Is it not probable that the impact of a column of blood moving with this velocity against a stationary column of blood will so distend the artery as to set it into vibration?

Preliminary correlation of the Korotkoff sounds with the water hammer hypothesis.. Be this as it may, it is interesting to correlate the phases of the Korotkoff sounds with water hammer action as we believe it manifests itself during the gradual decompression of an artery: (a) The first sound is heard at the instant the blood in the artery below the compression chamber shows a brusque acceleration with each pulse (1). (b) The intensity of the sound then increases through the second and third phases[2] as long as the diminishing compressing pressure still suffices to occlude the artery during a part of diastole. It is during this stage, we have shown above, that the energy liberated by the water hammer presumably is constantly increasing. (c) The sudden dulling and weakening of sound (fourth phase) occurs exactly at the instant the compressing pressure leaves the artery open during diastole (1). On the basis of the water hammer hypothesis this weakening is due not alone to a diminution in the velocity of flow into the compression chamber during systole but perhaps even more to the fact that the

[2] The special sounds of the second phase will not be considered for the present.

column of blood below is no longer stationary at the time it receives the impact, but is moving continually in the direction the impact tends to drive it. (d) Below the diastolic level of compression the sounds usually soon fade away (fifth phase). Even at this time, however, some water hammer action must still persist; for the artery in the compression chamber still increases in volume with each pulse more than does the uncompressed artery. The more rapid flow thus permitted in this part must be checked by the more slowly moving blood below. It is scarcely necessary to add that in those instances in which the pulse itself is brusque enough to elicit sound vibrations from the artery, the sounds will persist even when the artery is relieved of all compression.

The remainder of this paper is devoted to an exposition of the evidence proving this hypothesis and of the objections to other views that have been proposed to explain the Korotkoff sounds.

METHODS IN GENERAL

For the most part the experiments have been performed on dogs. The size of the animal was not of any particular consequence provided the legs were sufficiently long for our purpose. Morphine and ether were employed as anaesthetics in all cases. The ilio-femoral artery is dissected out from well up in the abdomen down to the origin of the *arteria saphena* and all of the branches are tied with fine silk close to their origin. In this way a long, perfectly straight, and unbranched artery is obtained. On the artery thus prepared the compression chamber (our arteriograph) (14) and the stethoscope are placed.[3]

The phonendoscope was used only for special purposes. This instrument can not be applied to the artery without partly compressing it and thus not alone interfering in an uncertain way with blood flow, but also tending of itself to sound production beyond. There was, however, still another reason for not using the phonendoscope in certain phases of the work. Owing to its extreme delicacy it may pick up sounds originating some distance from the spot to which it is applied. The dog's artery emits a sound when it is not compressed. Therefore the artery central of a region of complete occlusion emits a

[3] Never having had any difficulty with this arteriograph we are at a loss to understand Warfield's (15) lack of success with it. The apparatus finally used by Warfield in its stead, on account of its bulk and the necessity of holding it in place by hand, was wholly unsuited to our purposes.

sound. Under certain circumstances this sound is picked up by the phonendoscope even when it is applied over the artery below the occluded region. Furthermore, when the compression is such as to cause loud Korotkoff sounds, these may be heard by the phonendoscope over a very wide range; not alone over the artery below the arteriograph, but also over a wide zone of tissue to either side of it. It can be readily understood how the detection by the phonendoscope of sounds transmitted such distances from the place of their origin might, under certain circumstances, give rise to difficulty.

When there was danger that this property of the phonendoscope might give rise to confusion, we had recourse to an *artery stethoscope.* The bell of this stethoscope was of the usual form but was closed below by a plate which could be screwed to the bell. The artery passed through the stethoscope by two holes on opposite sides, bisected by the plane of junction of the plate with the bell. This stethoscope was used in all observations excepting where it is specifically stated to the contrary. The arteriograph and stethoscope are trued on the artery so that the latter passes accurately through the orifices of both and so that at no point is the artery pressed upon or bent, and both instruments are then rigidly fastened in place. The arteriograph is then connected by tubes with a mercury manometer, a sphygmomanometer or other recording mechanism, and with an inflating bulb. The stethoscope, for reasons which will be made clear later, was provided with an adjustable side opening.

In our study of the sound phases, we have placed our main reliance in the auditory method rather than in some method of recording sounds. It would seem that none of our recording mechanisms will do just what was demanded by this investigation. While for the exact determination of time relations a record is indispensable, changes in intensity or quality of sound often are not clearly indicated by the microphone. In the present case this difficulty is magnified by the fact that in the dog the sound never wholly disappears with decompression. The dangers of relying entirely upon the graphic method of recording sounds are illustrated by the experiments of Hooker and Southworth (16). These investigators employed the method of Einthoven and Geluk to record the sounds. In order to get only *sounds* by this method they found it necessary to adjust a side opening until deflections of the galvanometer were obtained only in the range of the pulses that produced audible sounds. Are we not to infer from this that the telephone transmitter is affected not alone by sound waves but also by

pressure waves, and that the adjusting of the side opening resulted in reducing the effect of the pressure waves until only those that were sufficiently strong to cause the artery to emit sounds also moved the diaphragm of the transmitter? Be this as it may, it is obvious that in the present experiments no such adjustment of a sound recording device was possible because there is no lower limit to sound production.

Nevertheless, in order to be in a position to determine time relations, we have in many of our experiments recorded sounds. The method employed, though a well-known one, we happened upon by chance. In some of our experiments a record was desired of the pulse passing through the arteriograph. As we wished to get this pulse before any of it was lost in transmission and as it was also necessary to attach the stethoscope as close as possible to the arteriograph, it was decided to arrange a sphygmograph within the stethoscope itself. The sphygmograph consisted of a receiving tambour connected with a delicate Frank mirror capsule. A channel in the floor of the stethoscope, of about the same width as the artery and covered with very delicate rubber dam, served as the receiving tambour. The channel paralleled the artery. The level of the rubber head covering it was such with respect to the lateral openings of the stethoscope that the artery in the stethoscope just rested lightly on it. It was found that this sphygmograph recorded not alone the pulse in the artery, but also most of the sound vibrations of the arterial wall. With this apparatus, therefore, the arterial pulse and certain of the arterial sounds may be recorded photographically while at the same time the sounds may be followed with the ear. It should be added that the pulse-recording part of this instrument was not delicate in the sense that it would detect the feeblest of pulses. As a matter of fact it often failed to indicate the very earliest of the pulses, pulses that could be faintly felt by the finger.

It has been stated that the stethoscope was provided with a lateral opening the size of which could be readily varied. This was provided for two reasons. In the first place, it was feared that the changes in the size of the artery with the pulse might so affect the pressure on the ear drums as to modify the quality or the loudness of the sounds heard. All danger of any such modification is eliminated by using the instrument with the lateral tube wide open. And in the second place, compression of the artery in the arteriograph is associated with variations in the calibre of the artery passing through the stethoscope. These variations are accompanied by variations in the width of the space around the artery where it enters and leaves the stethoscope. Such

variations might determine variations in the intensity of the sounds heard. They could be obviated by leaving the side tube open. The attempt was also made to eliminate them by filling with vaseline the crevices between the artery and the orifices of the stethoscope.

RESULTS

Description of the compression sounds

The sounds heard through the artery stethoscope while the pressure in the arteriograph is falling from a high to a low level are in all save one respect usually the same as those heard in man. With a sufficiently high pressure there is no sound whatever perceptible. If the pressure is permitted to fall slowly and steadily, a point is reached where a clear sound is heard, faintly at first, though distinctly, and rapidly increasing in intensity to the characteristic pistol shot sound. Then the sound becomes murmurish in quality, though the murmur is very distinctly accented at the beginning. Soon the murmur gives way to clear sounds which may become exceedingly intense and ringing. These intense sounds last for a short while and then become dull and fainter, rapidly at first, and then more and more slowly. The fainter sounds persist, however, even when there is no pressure whatever on the artery. Not infrequently a phase in which the sounds have a murmurish quality is lacking. All of these sounds, in properly prepared animals, are quite as loud as, indeed often louder than, those heard in man.

The photographic record of the sounds as obtained with the modified stethoscope bears out the ear as regards both intensity and pitch and in addition gives, roughly to be sure, the actual rate of vibrations, from which the position of the sounds in the musical scale can be determined.[4] It should be added that even in especially clear records the fainter sounds, namely those of the early first and later fourth phases, usually do not record. It is not to be expected that the pitch

[4] If proof is needed that the vibrations recorded by the tambour of the stethoscope are actually sound vibrations, it is furnished by the fact that the vibration rate varies in agreement with the changes in pitch as determined by the ear; that the variations in amplitude agree with the changes in intensity, excepting where marked changes in pitch tend to mask the effect intensity would otherwise have on the amplitude of the recorded vibrations; that the vibration period of the Frank mirror capsule differs from the rates recorded (by the Frank method it was 84 d.v. per second); and that vibrations are sometimes recorded when the apparatus receives no impact that could cause it to manifest its inherent period.

of the sounds will always be the same even in the same animal let alone different animals; nevertheless in our experience it has been fairly uniform. The rate of vibrations of the last of the third phase sounds has usually been 170 to 180 d.v. per second, that is to say, approximately f (172 d.v.) in the octave between c and c′. The first phase and early fourth phase sounds are distinctly lower in pitch; they are usually made up of vibrations at the rate of about 133 per second, and therefore closely approximate c (128 d.v.).

We have gained the impression that other investigators have not been so successful in the use of the dog's artery for the study of compressions sounds. Thus Lang and Manswetowa (17) state that the auscultatory method cannot be used on the leg of the dog. Warfield (15) attempted to differentiate the sound phases in the dog but found it difficult to do so on account of the faintness of the sounds. Again MacWilliam, Melvin and Murray (18) say that "in the case of small animals, the testing of the auditory method is not satisfactory." They evidently found it necessary to use the sheep as the subject of their experiments. By our method the sounds are loud and the phases easily distinguishable in animals no larger, for instance, than the fox terrier.

It has been stated above that in the dog the uncompressed artery always emits a distinct though faint and dull sound. Warfield (15) has also heard a sound in the uncompressed dog's femoral, though not constantly. It should be added that the sound we have heard is not the result of the preparation to which the artery is subjected, for it can be clearly heard through the tissues in the normal, unoperated animal. It might be noted here that the uncompressed dog's carotid artery, as well as that of man (19), normally emits two sounds. The origin of these sounds is still a matter of conjecture. Rarely the uncompressed femoral artery of the dog also emits two sounds. This has not, however, occurred sufficiently constantly to allow of an investigation of the phenomenon.

Inasmuch as the uncompressed femoral artery of the dog usually emits a sound it might be suspected that the first sound heard while decompressing is transmitted from above and does not originate in or below the compression chamber. All of the evidence is, however, opposed to this view. In the first place the qualities of the two sounds are entirely different. These differences in quality are not due to the fact that the normal sound is emitted by a full artery and the first Korotkoff sound by a relatively empty artery. For if the artery is occluded below the stethoscope and consequently remains full at all times the first phase

sounds still differ in quality from the sound that is heard when the compression pressure is abruptly dropped to zero while the artery remains occluded below. More to the point, however, is the fact that during the early sound phases the sound emitted by the artery above the arteriograph is earlier in the pulse cycle than the Korotkoff sounds. To demonstrate this time relation it is merely necessary to listen to the sounds that can be heard through the phonendoscope applied to the artery below the arteriograph. When the compression pressure exceeds the systolic pressure a sound can often still be heard. This sound is, as has been said, transmitted through the tissues and picked up by the delicate phonendoscope. Now when the sounds are in their first phase, the characteristic Korotkoff sound is heard to distinctly follow by a perceptible interval the sound coming from above.

The bare artery suffices for sound production

The fact, brought out in the preceding section, that the compression sounds obtainable from the bare artery of the dog are perfectly characteristic and rival in intensity those obtainable by the usual method in man, demonstrates conclusively that any other conditions than those obtaining in the present experiments are not essential to the production of the Korotkoff sounds. The contention of Hill and co-workers (6) that all of the compressed arteries "big and small" and "every patent arteriole" under the armlet participate in the production of the sound and that the "whole range of sound is dependent on the resonating effect of the vessels and the tissues surrounding the artery" in the light of this observation loses much of its force. Nor is it necessary to assign any significance, as do these authors, to the presence in the compression chamber of a "tense resonating mass of tissue" that the "impact of the systolic wave" sets into vibration. In the absence of any experimental evidence that these are essential factors in sound production we are justified for the present in concluding that the presence of a large artery of a living animal in a compression chamber furnishes all of the conditions necessary for the production of characteristic Korotkoff sounds.

Is resonance of the compression chamber a factor?

It has been suggested by Gittings (8) that the compression chamber, by acting as a resonator, materially enhances the sounds produced by the tensing of the arterial walls just without the compression chamber. In this connection MacWilliam and Melvin (5) found that the sounds

"are quite well marked" when the compression chamber and connecting tubes of a pulsating schema are filled with liquid. They therefore set aside resonance as a factor in the mechanism of sound production. This conclusion is not, however, justified by their experiment, for apparently they did not determine whether filling the compression chamber with water *modifies* the sounds; not even Gittings maintains that resonance is the sole factor.

For the purpose of determining whether resonance is a factor we have compared the sounds yielded by a compression chamber which might resonate, with those yielded by the same compression chamber so modified that it could not resonate. The compression chamber in these experiments consisted of the arteriograph, a one litre glass bottle and connecting tubing, all air filled. In order to abolish the resonance of the arteriograph it was, at the desired time, completely filled with water; and in order to effectually prevent any such resonance as the other parts of the compression chamber might possess from acting back upon the artery, a fairly tight plug of cotton wool was inserted into the neck of the arteriograph just above the level of the water in it. This plug, it is needless to say, did not interfere with the rapid equalization of pressure throughout the compression chamber.

With this apparatus it was found that as a rule filling the arteriograph with water, and thus eliminating its resonance, did not change appreciably either the quality of the arterial sounds or their intensity, as heard while the arteriograph was air-filled. It should be borne in mind that these observations can be made only qualitatively, as a considerable interval of time elapses between the successive determinations. Occasionally, filling the arteriograph with water seems to suppress the earliest of the first phase sounds. Inasmuch, however, as the same result is obtained by merely reducing the size of the air space in such a way as not to alter its resonance (see below), it seems justifiable not to attribute this reduction of sound to the elimination of resonance; especially in view of the fact that a perfectly satisfactory explanation of this reduction is found in the retarding effect the water exerts, by virtue of its inertia, on the initial velocity of the blood entering the opening artery.

Influence of the size of the compression chamber on sound production

So far as we have been able to determine, Gittings bases his belief that the compression chamber acts as a resonator merely upon the observation that when the compression is effected by means of an Es-

march bandage the arterial sounds are either absent or very faint. The same result is obtained, it should be added, when the artery is compressed with the thumb (5). This observation is open, however, to a wholly different interpretation. The Esmarch bandage exerts upon the artery a compression which, compared with that exerted by the air chamber of a sphygmomanometer, has a very low grade of compressibility. With the advent of the pulse, the artery cannot open out to the size it attains in a chamber of high compressibility. The velocity of flow and the rate of transmission of the pulse, two of the important factors determining water hammer action, will therefore be diminished.

The effects on the Korotkoff sounds of limiting the compressibility of the compression chamber have been investigated by inserting a glass stopcock in the course of a vertical glass tube connecting the arteriograph with the manometer and bottle of the apparatus just described above. By turning the stopcock the size of the compression chamber could suddenly be changed from that of the arteriograph alone to that of the arteriograph plus bottle and connecting tubes, or vice versa. A large (1 litre) bottle was used in these experiments so as to render possible a wide range of compressibility. The phase of the pulse cycle in which this change was effected might have been, though it was not, determined in this particular set of experiments. In another series of observations, however, in which the arteriograph was filled with water up to about the level of the stopcock, so as to make possible an extreme diminution in the compressibility of the compression space, the phase of the pulse cycle in which the compression chamber was made small could be determined by noting the level at which the pulsating water in the vertical tube was caught by the closing of the stopcock. In the case of the water-filled arteriograph, it will be noted, the compressibility of the compression space when the stopcock is closed is limited practically to a very slight bulging of the rubber membrane out of the orifices of the arteriograph. It should be added that in order to eliminate any effect that might possibly be exerted through changing resonance of the compression chamber, a cotton plug was again inserted in the glass tube just above the stopcock.

Experiments with the water-filled arteriograph. It is convenient to consider first the experiments in which the changes in compressibility were effected by turning the stopcock of the water-filled arteriograph. In this case the changes in compressibility are extreme. As might have been predicted from an analysis, in the light of the water hammer hypothesis, of related data as given in the first paper of this series, the

result obtained depends to some extent upon the phase of the auscultatory phenomenon, and upon the phase of the pulse cycle obtaining at the time the stopcock is closed. In the early sound phases, that is, while the extra-arterial pressure is still relatively high, closing the stopcock, and thus reducing compressibility to a minimum, at once stops all sound, irrespective of the phase of the pulse cycle in which the change is made. At lower extra-arterial pressures, when the sounds are intense (third phase), closing the stopcock either stops all distal sound or causes it to diminish markedly in intensity. The sound always disappears when the closing stopcock catches the meniscus of the water low in the vertical tube of the arteriograph, that is, when it catches the pulse in its diastolic phase. The loudest of the sounds heard with the reduced arteriograph occur when the stopcock catches the meniscus high in the vertical tube, that is when the pulse is in its systolic phase.

This enfeeblement of sound, amounting at the higher compressing pressures to a complete disappearance, is attributable on the basis of the water hammer hypothesis mainly to the limitation of the pulsatile increase in volume, and therefore of the velocity of flow, in the compressed artery, resulting from the splinting of the arterial walls by the markedly reduced compressibility of the compression space. This effect is much more marked when the reduction in the compressibility is effected during diastole, probably on account of the tendency on the part of the confined space to hold the artery closed during the entire pulse cycle.

Experiments with the air-filled arteriograph. When the arteriograph is emptied of water, closing the stopcock still diminishes the compressibility of the compression space, but not nearly to the same extent as in the preceding experiments. Owing to differences in the quality and loudness of the sounds in different animals and to differences probably attributable to variations in the size of the artery relative to the arteriograph, it is difficult to give a categorical account of the changes in the sounds resulting from reducing the size of the air space around the artery. The difficulties may be illustrated by giving in tabular form some of the results obtained (see Table I). But despite variations in different experiments the table does show a certain regularity in the results. Thus, reducing the size of the air chamber while first phase, and occasionally even while early second, phase sounds are heard nearly always causes them to disappear. By these means the compressing pressure at which the first sounds appear may be lowered by as much as 15 or even 30 mm. of mercury. The effect of reducing the size of the

TABLE I

Showing the effect on sounds of reducing the air space of the compression chamber

<table>
<tr><th>SOUND PHASE</th><th>EXPERIMENT 6</th><th>EXPERIMENT 7</th><th>EXPERIMENT 9 EARLY</th><th>EXPERIMENT 9 LATE</th></tr>
<tr><td>First early</td><td rowspan="2">Disappear</td><td rowspan="2">Disappear</td><td rowspan="2">Disappear</td><td>Disappear</td></tr>
<tr><td>First late</td><td>Fainter</td></tr>
<tr><td>Second early</td><td>Murmur disappears and sounds become snapping and fainter</td><td>Disappear</td><td rowspan="2">Sometimes louder, sometimes fainter *</td><td rowspan="2">Sometimes louder, sometimes fainter *</td></tr>
<tr><td>Second late</td><td>Murmur disappears and sounds become snapping without change in intensity</td><td>Disappear(?)</td></tr>
<tr><td>Third early</td><td rowspan="2">Sometimes the murmur reappears; if not, sounds become louder</td><td>Sometimes louder, sometimes fainter</td><td>No change in intensity</td><td></td></tr>
<tr><td>Third late</td><td>No change</td><td>Fainter</td><td>Always fainter</td></tr>
<tr><td>Fourth</td><td>No change</td><td>No change</td><td>Fainter</td><td></td></tr>
</table>

* No second phase sounds.

air chamber during the second phase depends presumably upon the phase of the pulse cycle in which the reduction is made to take place—the sounds sometimes becoming fainter, sometimes louder; sometimes the blowing sound disappears. In the third phase the sounds usually become fainter though they may not be changed, or may rarely become louder; when the second phase is especially well developed, diminishing the size of the air chamber during the third phase may cause second phase sounds to return. During the fourth phase the sounds usually are not appreciably altered; occasionally they become slightly fainter.

It will be noted that at the higher compressing pressures the results (disappearance or reduction of sound) obtained upon reducing compressibility are qualitatively, though not quantitatively alike with both the water and the air-filled arteriographs. This statement applies also to the effect upon sound of closing the stopcock, presumably during diastole, at all lower compressing pressures. The result of closing the stopcock presumably during systole is, however, wholly different: the sound in the case of the air-filled chamber may actually become louder than that heard while the compression chamber is large. To explain this result we find it necessary to have recourse to an additional factor. At the lower compressing pressures closing the stopcock, while reducing the compressibility of the compression space, has not anything like so marked an effect upon it as at higher compressing pressures. Under such circumstances it is conceivable that the effect the closing of the stopcock in different phases of the pulse cycle has upon the mean compressing pressure may become more significant relatively than all the other effects. It is clear that when the stopcock in closing catches the artery expanded by the pulse, the mean level of the compressing pressure will be lowered slightly; and that when the artery is caught in its collapsed condition, the mean level will be raised: in other words, the compressing pressure in effect is lowered or raised, respectively. The effect upon sound production of closing the stopcock at low compressing pressures, it will be noted upon consulting the Table I, is consistent with the premises. When the stopcock is closed while the compressing pressure lies in a region where, say, a slight *decrease* in its level would cause a comparatively marked change in the intensity of the sound, say, an *increase*, and while, say, systole prevails, the loudness of the sound would increase. And when under exactly the same circumstances the stopcock is closed during diastole the loudness of the sound would *decrease*. If, however, the stopcock is closed again at a time when a slight *decrease* in the level of the compressing pressure causes a *decrease* in sound intensity, the changes in the intensity of the sound would be just the reverse of those mentioned above.

In conclusion it is important to bear in mind that the changes in intensity of sound noted in the foregoing experiments can not be attributed to changes in resonance, the cotton plug just above the stopcock having the effect of keeping the resonating properties of the arteriograph constant throughout the experiment. The effects upon sound production of limiting the compressibility of the arteriograph,

it will be noted, are similar to the effects of compressing the artery with an Esmarch bandage or with the thumb. Inasmuch as the former are not attributable to resonance changes but rather to a limitation of compressibility, it seems justifiable to conclude that the same explanation applies to the latter also.

Is the artery beyond the compression chamber essential for the production of sound?

The observation of MacWilliam and Melvin to the effect that compression "sounds are perfectly well developed and characteristic" when the phonendoscope is applied over the glass tube issuing from the artery in the compression tube of their circulation schema even when there is no artery beyond, answers this question in so far as it applies to an artificial circulation. We have confirmed this observation in animal experiments. We find that occluding the artery in the lower neck of the arteriograph by thrusting into the latter a nicely rounded glass rod to a depth of some 4 to 6 mm. in such a way as to compress the artery against the side wall of the neck, does not cause the sounds that can be heard by placing a phonendoscope on the arteriograph to cease. We can go further and add that thus occluding the artery fails to alter in any marked degree the character of the sounds heard: they sometimes become slightly louder, sometimes slightly fainter.

In this connection it is necessary to bear in mind the possibility that the part of the artery within the compression chamber forming the transition between the part collapsed, in the middle regions, and the part uncompressed, just at the lower edge of the compression chamber, may be a factor in sound production. MacWilliam and Melvin, we assume, believe they eliminated this possibility by treating the lower part of their arteries with formalin. We do not, however, understand how such treatment succeeded in removing the lower conical closure. It was in an effort to accomplish this that we employed a glass rod and pushed it alongside the artery from without rather than into the lumen of the artery, instead of merely blocking the artery in the usual way at the point where it issues from the arteriograph. Yet we cannot be absolutely certain that even by this procedure we succeeded in completely eliminating this factor; for some blood is bound to be trapped between the compressed and the occluded segment when the artery closes under the compression. It would seem, however, that an objection on this basis to the conclusion that the distal artery

is not essential to the production of compression sounds would be rather far-fetched.

The fact that the artery beyond the compression chamber is not essential to sound production obviously throws out of court all explanations of sound production based on the injection of blood into an empty artery. On the other hand, it is clear that eliminating the artery beyond does not reduce the factors that determine the magnitude of water hammer pressure.

Does the artery beyond the compression chamber contribute to sound production?

It has been shown that the artery beyond the compression chamber is not essential to sound production. This observation does not, however, preclude the possibility of sound production in the lower artery also; for it is conceivable that the impact that first produces sound may be propagated by the blood in sufficient amplitude to continue to produce sound for some distance along the artery. Indeed it will be demonstrated later that during the louder sound phases the arterial walls for some distance below the compression chamber are stretched unusually sharply by each pulse. The interest that attaches to this question lies mainly in its bearing on those views that limit sound production to the compression chamber. If the Korotkoff sounds are produced alone by a change in the form of the tube in the compression chamber (5), or by "a tense resonating mass of tissue" in the compression chamber which is set into vibration by the "impact of the systolic wave" (6), the sound would be propagated from that place as sound through the blood and the tissues. If so, it should be possible to hear the propagated sound quite as well over, say, a metal tube intercalated in the course of the peripheral artery as over the artery itself. On the other hand, if the sound heard along the course of the artery below the compression chamber is produced by a propagated impact that induces sound as it proceeds, an intercalated, inextensible tube should not give out the same sound as the artery immediately above and below it.

In order to put this question to the test of experiment, the effect on the arterial sounds has been determined of causing a paraffined, metal tube 4.5 cm. long to replace the same length of artery, beginning about 4.5 cm. below the compression chamber. Then the segment of artery between the compression chamber and this tube, the tube itself, and finally the artery just below the tube, were in succession placed in the

stethoscope. The crevices between the artery and the opening into the stethoscope were filled as thoroughly as possible with vaseline and the side tube of the stethoscope was left wide open. It was found that in the third phase the sounds were loudest close to the arteriograph and faintest over the tube, where the sounds, when present at all, were feeble and distant. Presumably, therefore, we are dealing here, in large part, at least, with a propagated impact that produces sound locally as it proceeds, though to a certain extent the transmission of sound as sound also takes place. It should be added that the phonendoscope detects over the metal tube a fairly loud sound. In view, however, of the delicacy of the phonendoscope, referred to above, it seems fair to assume that in this case it is picking up a transmitted sound.

Configuration of the compression pulse

Records have been made of the compression pulse, that is, of the pressure changes in the compression chamber produced by the pulse, by connecting the arteriograph, through a 0.5 or 1 L. air-filled bottle, either with the Erlanger sphygmomanometer provided with a Frank mirror capsule in the place of the usual tambour, or with a Frank mirror capsule directly. Records have been made both by the method of intermittent escapement, when as a rule the pinhole in the recording tambour was closed, and by the method of continuous escapement. The records made through the Erlanger sphygmomanometer are more ample and therefore have more fling than those made directly through the Frank capsule; this has been an aid in the analysis of the records rather than a detriment, because the presence of a certain amount of fling brings out more sharply changes from one pressure gradient to another.

In the preceding paper these records were analyzed as regards the amplitude of the oscillations, and its relation to the moment the artery during decompression begins to open momentarily with each pulse, and later ceases to close. It was stated in that paper that the first sound is heard presumably the instant the artery opens momentarily, and that the dulling of sound agrees exactly with the pulse with which the artery fails to close. Here we are interested in determining whether the configuration of the individual compression pulse is in agreement with the water hammer hypothesis.

We may first ask, what influence would we expect water hammer to exert on the configuration of the compression pulse? It has been

shown (1) that the compression pulse can be produced only by volume changes that are extensive enough to compress the air in the chamber to the pressures of the compression pulse. Therefore, to be in a position to answer the above question, it is necessary to know something with regard to the volume changes determined by water hammer. So far as I know, the volume changes produced by water hammer have never been recorded. However, from the theory of water hammer as developed by Russell (9), the volume changes may be derived as follows:

If we regard the column of water as divided into successive laminae, the lamina that meets with the obstruction is stopped, crowds up against it and is compressed by virtue of its own kinetic energy. As it is compressed, the ring of pipe wall surrounding it is distended. While this lamina is being compressed and shortened the next lamina behind it follows on with undiminished velocity, until the compression of the first lamina is complete. It in turn then suffers retardation and compression, at the same time stretching the pipe wall around it. Other laminae follow in succession so that in a very short time the pipe is distended back a considerable distance. In other words, one effect of water hammer is to distend the tube backwards from the point of impact.

Therefore water hammer would distend the artery first under the lower edge of the compression chamber. This distention would, however, extend rapidly back past the upper edge of the chamber where, so far as concerns the compression pulse, distention due to water hammer per se would cease abruptly. Then, provided the vibrations set up in the blood column have ceased, the pressure head of the pulse proper alone would determine further volume changes of the compressed artery. The compression pulse up to the crest of the pulse proper, for the sake of convenience, might on this basis be divided into three periods, namely:

a. A period included between the onset of the pulse and the forcing open of the artery in the compression chamber, during which the upper conical closure would be filling with blood and the pressure in the chamber would therefore be increasing at a rate proportional to the rise of pressure with the pulse.

b. The second period would be coterminous with water hammer as described above. The rate and amplitude of the rise of pressure would presumably be determined by the force of the water hammer. In case the backward distention of the artery reached beyond the upper edge

of the compression chamber this period of the rise of the compression pulse presumably would be at a more or less uniform rate up to an abrupt termination.

c. The third period would be distinguishable from the second only if water hammer action were completed before the pulse proper had attained its crest. Then there would be two crests, the first, due to water hammer, terminating the end of a rise that is uniform in rate and appearing earlier and earlier in the compression pulse, the second terminating a gradient partaking of the form of the corresponding part of the pulse and appearing at a constant time interval after the beginning of the compression pulse.

Let us then examine a typical record (fig. 1, Table II) with the theory of the volume changes produced by water hammer in mind, assuming for the present that water hammer is active as long as the sounds are louder than those emitted by the uncompressed artery.

1. When the sounds first begin to come through, the only recognizable change in the anacrotic limb of the compression pulse is an increase in amplitude. This is not inconsistent with the hypothesis, for the first opening of the artery during decompression is very brief in duration and occurs so close to the crest of the pulse proper that period *a* (see above) is merged with period *b*, while there is no period *c* distinguishable from period *b*. In other words, all that we could expect at this time is an increase in the amplitude of the pulse.

2. After the compressing pressure has fallen a very few millimeters of mercury below the level at which the sounds first became audible, the compression pulse begins to show a double crest. The first of these crests, which presumably terminates period *b*, soon becomes very distinct and develops into an obvious fling; and it remains distinct until the sounds begin to diminish in intensity, when, within a very few pulse beats, it can be recognized only with difficulty. From the time the first crest becomes well marked, and until it begins to diminish in clearness, the upper part of the rise of pressure that leads to it occurs along a straight line. There is, however, no mark on the rise of the compression pulse that is sharp enough to be of use in distinguishing between the curved line belonging presumably to period *a* and the straight line belonging presumably to period *b*. The first crest is attained earlier and earlier in the pulse as the compression diminishes.

3. It is sometimes difficult to decide upon a point on the compression pulse that can be regarded as its true crest, because this part of

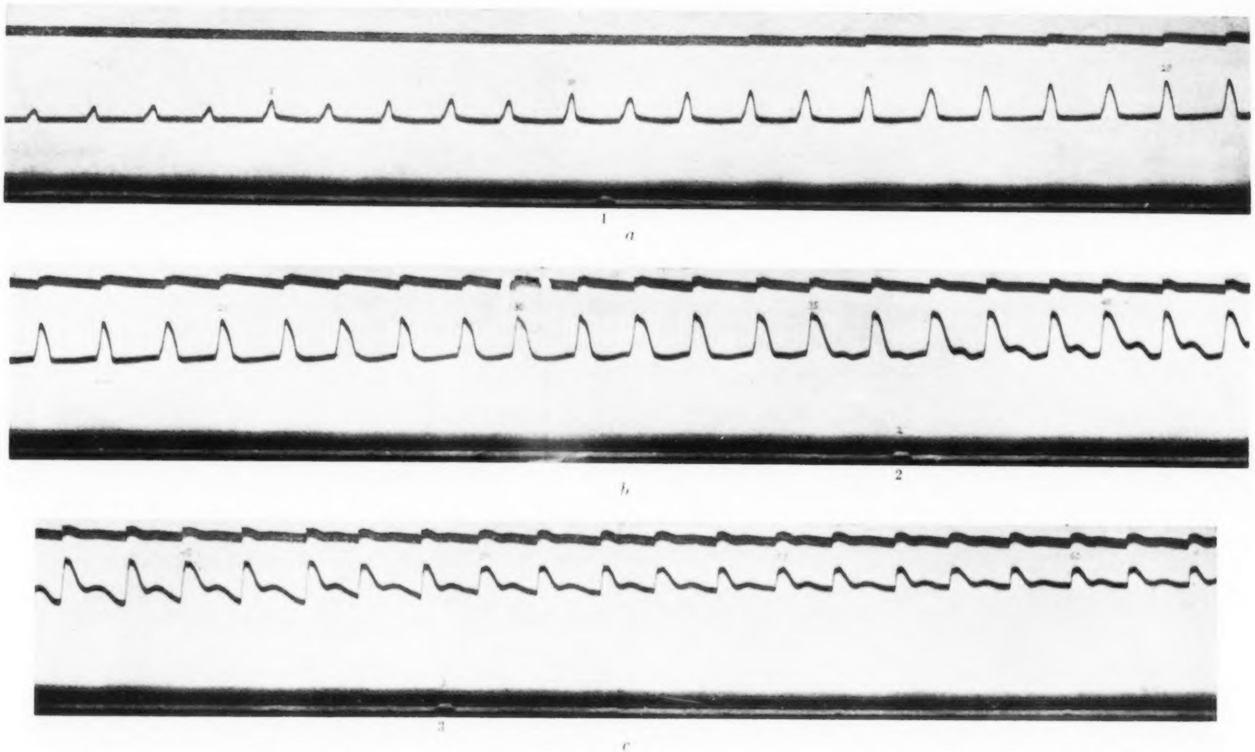

Fig. 1. *a, b, c*. Record from the femoral artery of the dog while decompressing by the continuous method. Reduced to ¼ size. Read from left to right. Upper tracing: arterial pulse and sounds just beyond the compression chamber, by the recording stethoscope; middle tracing. compression pulse; lower tracing: time in fifths of seconds and signal. (1) First signal, sound becomes audible. (2) Second signal, sound becomes intense. (3) Third signal, sound becomes dull.

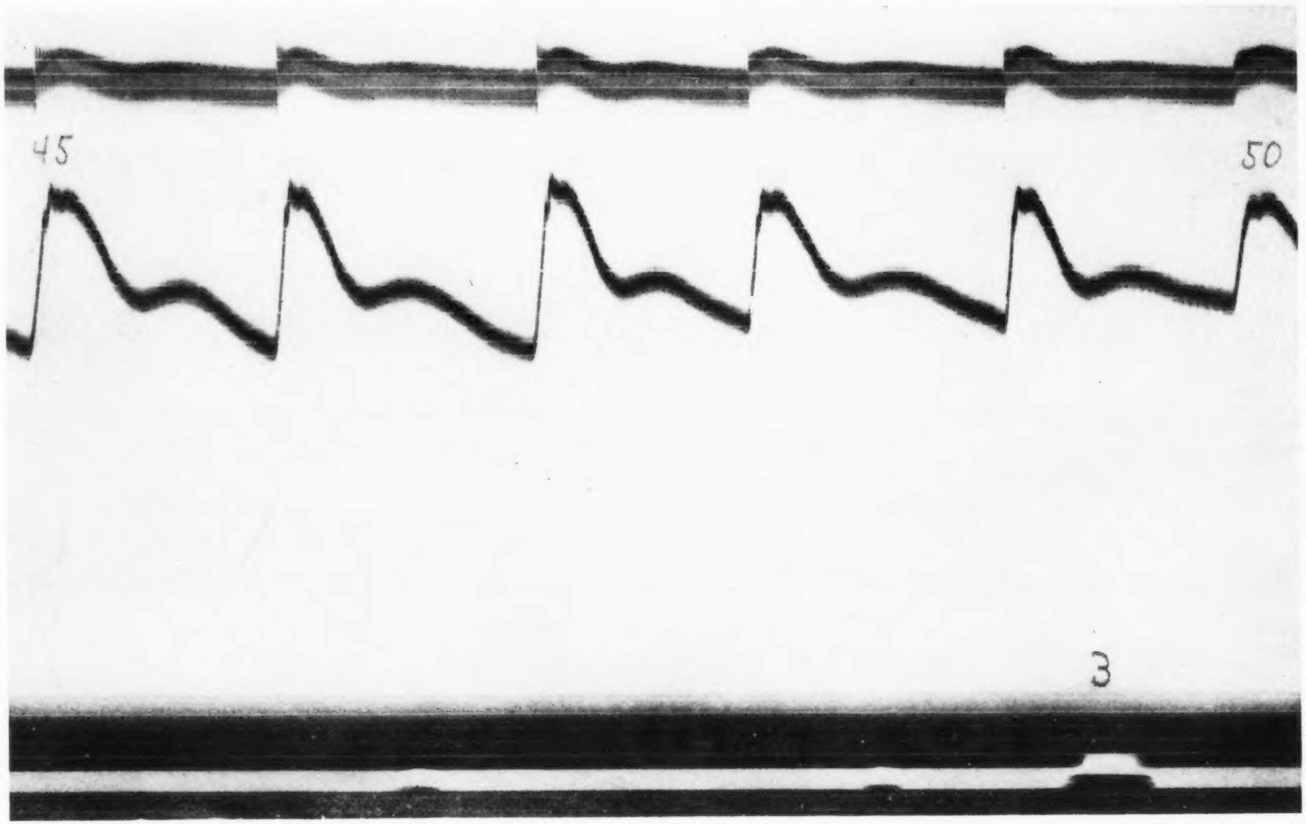

Fig. 2. Section of figure 1 (pulses 45 to 50 inclusive), reproduced in full size to show details.

TABLE II

Analysis of figure 1

(1)	(2)	(3)	PERIPHERAL PULSE			COMPRESSION PULSE				(11)
NUMBER OF PULSE *	TOTAL AMPLITUDE	DURATION OF PULSE CYCLE†	(4) Time to	(5) Amplitude of first crest‡	(6) Amplitude of second crest	(7) Amplitude of first crest	(8) Time to first crest	(9) Time from sound to top of first crest	(10) Amplitude from sound to top of first crest	RATIO Col. 10 / Col. 9
	mm.	*sec.*	*sec.*	*mm.*	*mm.*	*mm.*	*sec.*	*sec.*	*mm.*	
1	4.5	0.53								
2	6.5	0.50								
3	7.5	0.51								
4	6.5	0.53								
5	10.5	0.50								
6	9.0	0.54								
7	11.0	0.54								
8	12.5	0.51								
9	11.5	0.56								
10§	16.0	0.50	0.071		1.0			0.015	2.5	167
11	13.5	0.52			—?					
12	16.0	0.54	0.063	0.5	1.0			0.019	2.5	131
13	17.0	0.50	0.071	0.6	1.2	17.0	0.082	0.02	3.5	175
14	16.5	0.56	0.071		1.0			0.02	3.5	175
15	18.5	0.53	0.060	1.0	1.4	18.0	0.071	0.019	4.0	210
16	18.0	0.51	0.079	1.0-	1.3	17.5	0.097	0.019	3.0	158
17	19.5	0.57	0.059	1.2	1.5	18.0	0.075	0.02	4.0	200
18	20.0	0.51	0.056	1.3	1.4	19.0	0.069	0.02	4.0	200
19	19.0	0.53	0.066	1.4	1.4	18.0	0.082	0.019	3.5	184
20	20.5	0.56	0.053	1.8	2.0	19.0+	0.065	0.019	5.0	264
21	20.5	0.49	0.054	1.8	2.3	19.0	0.065	0.02	6.5	325
22	21.0	0.55	0.048	2.2	2.8	20.0	0.063	0.019	6.5	312
23	22.0	0.54	0.048	3.0	3.4	20.5	0.057	0.018	7.0	389
24	21.0	0.49	0.057	2.2	3.0	20.0	0.075	0.019	6.0	316
25	22.5	0.57	0.043	2.5	3.5	21.0	0.060	0.022	7.0	318
26	22.0	0.49	0.043	2.8	3.0	21.0–	0.060	0.02	7.5	375
27	22.0	0.54	0.046	2.8	3.0	21.0	0.065	0.022	8.0	364
28	23.0	0.54	0.038	3.0	3.2	21.3	0.053	0.022	10.0	455
29	22.0	0.47	0.043	3.0	3.4	21.0	0.057	0.019	8.5	447
30	23.0	0.55	0.037	3.0	3.2	21.5	0.053	0.02	9.5	475
31	23.0	0.49	0.035	3.3	3.3	22.0	0.049	0.02	11.0	550
32	23.0	0.53	0.043	3.3	3.3	21.5	0.057	0.02	10.0	500
33	23.5	0.56	0.032	4.0	3.4	22.0	0.046	0.019	11.5	579
34	23.5	0.47	0.034	3.8	3.5	21.5	0.049	0.022	11.5	546
35	24.0	0.55	0.035	4.0	3.5	21.5	0.053	0.023	12.0	522
36¶	24.0	0.51	0.028	4.0	3.8	22.0	0.046	0.019	12.0	632
37	24.0	0.51	0.038	4.0	3.4	22.0+	0.056	0.018	11.0	611

TABLE II—Continued

(1)	(2)	(3)	PERIPHERAL PULSE			COMPRESSION PULSE				(11)
NUMBER OF PULSE *	TOTAL AMPLITUDE	DURATION OF PULSE CYCLE†	(4) Time to††	(5) Amplitude of first crest‡	(6) Amplitude of second crest	(7) Amplitude of first crest	(8) Time to first crest	(9) Time from sound to top of first crest	(10) Amplitude from sound to top of first crest	RATIO $\frac{\text{Col. 10}}{\text{Col. 9}}$
	mm.	sec.	sec.	mm.	mm.	mm.	sec.	sec.	mm.	
38	25.0	0.56	0.026	4.2	3.7	22.0+	0.044	0.019	13.0	684
39	25.5	0.46	0.028	4.2	3.3	22.5	0.043	0.018	13.0	722
40	26.0	0.54	0.026	4.0	3.3	22.0+	0.043	0.019	14.0	737
41	26.0	0.55	0.025	4.0	3.3	22.0+	0.040	0.016	14.0	875
42	27.0	0.48	0.028	4.0	3.3	22.0+	0.044	0.018	12.0	667
43	26.0	0.57	0.025	3.8	3.0	21.5	0.047	0.015	13.0	867
44	26.5	0.49	0.024	4.2	3.3	21.5	0.035	0.015	13.0	867
45	23.0	0.54	0.024	4.0	3.0	19.0−	0.044	0.016	12.5	781
46	23.5	0.56	0.019	4.2	3.3	19.0+	0.037	0.015	15.0	1000
47	24.5	0.49	0.021	4.3	3.3	20.5	0.035	0.016	15.5	969
48**	19.0	0.56	0.013	3.3	3.3	15.0	0.029	0.016	12.0	750
49	18.5	0.50	0.012	3.3	3.3	15.0	0.029	0.019	13.0	684
50	14.0	0.51	0.013		3.4	?		0.022+	10.0	455
51	14.5	0.50	0.010		3.6	?				
52	15.0	0.46	0.012		3.7					
53	13.0	0.49	0.009		3.5					
54	13.0	0.53	0.009		3.6					
55	11.0	0.50	0.008		3.5					
56	11.0	0.56	0.006		3.8					
57	11.5	0.49	0.004		3.8					
58	10.0	0.53	0.003		3.6					
59	10.0	0.54	0.003		3.8					
60	9.5	0.50	0.004		3.7					
61	9.0	0.54	0.003		3.7					
62	9.0		0.003		3.7					

* The mean rate of pressure decrease is 2.2 mm. Hg per pulse; the rate in the vicinity of the systolic and diastolic pressures is approximately 2.5 + mm. Hg and 1.9 − mm. Hg per pulse respectively.

† The time was recorded in seconds. The paper, however, moved very uniformly at the rate of 68 mm. per second.

‡ The amplitude of the sound vibrations is always proportional to this rise.

§ First sound signalled.

¶ Signalled sounds intense.

** Signalled sounds fainter.

†† The figures given in this column opposite pulses 53 to 62 inclusive, were printed incorrectly in the preceding paper (1, p. 431). We are availing ourselves of this opportunity to indicate that another decimal place should be added to the corresponding figures as they appear in that paper in column "Time to peripheral pulse" in Table II, "Dog No. 10."

the curve not infrequently is made up of a series of waves such as commonly follow the first impact of water hammer. When, however, the records are clear in this respect the second crest continues to appear at approximately a constant interval after the pulse—an interval which is the same as that of the single crest seen in the earliest of the compression pulses. Between the first and second crests the gradient of pressure seems to be determined mainly by the phase of the pulse cycle that is to say, by the head of pressure, that has its course to run at that time.

Relation of the sounds to the compression pulse

In this connection it will be convenient to consider first the general configuration of the phonograms. It has been stated that during decompression the first audible sounds often do not record. In clear records, however, the sound waves appear before the compressing pressure has fallen from 8 to 10 mm. of mercury below the point at which the sounds become audible; at this time the sounds are still in the first phase. The amplitude of the sound waves, as has been said, changes in agreement with the intensity of the sounds as heard. The sound waves occupy the very beginning of the peripheral pulse (see below). In the early sound phases (see fig. 1), the first vibration of each group composing a sound is the highest, the subsequent waves diminishing rapidly in amplitude until they become indistinguishable. Later, when the sounds become intense, it is usually possible to make out a very small sound vibration preceding the peripheral pulse (see fig. 2). This preliminary vibration leads up to the powerful vibrations which are coincident with the beginning of the peripheral pulse. We are inclined to believe that the preliminary vibration is produced by sound transmitted by the blood stream as such, from the point where sound first originates, and that the powerful vibrations represent sound waves started locally within the stethoscope by the arrival there of a transmitted impact. Other explanations are, of course, possible. Assuming, however, that the explanation here offered is correct, it is of interest to attempt to locate by calculation, upon the basis of it, the seat of earliest sound production. The preliminary wave precedes the fully developed wave by roughly 0.005 second. It is, we assume, propagated with the velocity of sound and therefore without any appreciable loss of time. The impact would, however, be transmitted as a pulse wave along an artery that is practically under no tension what-

ever. The rate with which it is transmitted would therefore be very much slower than that of the pulse under normal conditions. Let us assume that it moves at a rate of 4 M. per second, that is, at about one-half the normal rate. Then the first seat of sound production would be located ($400 \text{ cm.} = \frac{d}{0.005''}$) 2 cm. above the tambour in the stethoscope. As our apparatus was arranged, this would place the origin of the sound in the lower part of the compression chamber just about where we would expect a water hammer to strike. We have assumed that the first fully developed sound wave marks the same event in all pulses. In order to locate on the compression pulse the point corresponding with the beginning of sound we have, in measuring our records, first determined the relation of the fully developed wave to the compression pulse, and have then carried all points thus located on the compression pulse forward by the duration of the preliminary wave, usually 0.005 second.

The fact that the first fully developed vibration is always the highest and that the sound vibrations succeeding it gradually fade away and have completely disappeared usually before the peripheral pulse has attained its true crest, proves that the sound is produced by a sudden impact in the earliest phase of the rise of pressure that lets the pulse through, and that it is not due to the continued stretching of the arterial walls through the anacrotic phase of the pulse.

If the compression sounds are produced by water hammer they should occur while the water hammer is acting and, in general, their intensity should be proportional to the force of the water hammer. Simultaneous records of the sounds in the artery beyond the compression chamber and of the compression pulse show that this is actually the case (see figs. 1 and 2). The sounds, measured as indicated above, always begin before the termination of the first abrupt rise of the compression pulse where this occurs; indeed it almost seems that they mark the point on the rise where the ascent begins to become straight (see preceding section). In the earlier pulses where the abrupt rise is not clear, the sounds begin a bit before the crest of the compression pulse.

This is exactly in accordance with the requirements of the hypothesis. The very first blood that succeeds in opening up the artery is stopped, distends the artery and produces the sound, while the artery then continues to distend backward. If this assumption is justifiable, we have in the peak at the top of the first rise of the compression

pulse, an index to the termination of water hammer. The intensity of water hammer would then be measured roughly by the ratio of the amplitude of the part of the compression pulse subtended by these two marks (sound and first crest) to the time elapsing between them. This ratio, given in column 11 of Table II, barring certain fluctuations which are in part due to the wide limit of error of measurement and in part to fluctuations in the circulatory conditions (see below), increases steadily from the time the sounds are first heard until they begin to diminish in intensity. With this diminution, the ratio rapidly falls off, although it can be determined through only a few of the succeeding pulses, the marks of water hammer soon becoming indistinguishable. The amplitude of the recorded sound vibrations varies in general as the magnitude of this ratio (see Table II, col. 5). It might be added that these variations furnish presumptive evidence in favor of the conclusion, reached in connection with the introductory theoretical discussion of the water hammer hypothesis, that water hammer increases during decompression until the artery remains open throughout the pulse cycle.

It has been stated that the water hammer ratio shows some fluctuations. When one examines the phonograms corresponding with the lowest ratios, namely, those obtained from pulses 18, 24, 25, 27, 32, 35, 37, 42 and 45 (Table II and fig. 1; also pulse 45, fig. 2), it is seen that the rate of vibration is invariably slower with these pulses than with any of the others. The amplitude of the vibrations, though, is not very different. Since, however, smaller vibrations of the same real amplitude should, as a result of instrumental error, be recorded larger than quicker vibrations, it seems justifiable to conclude that these particular sounds are lower, not alone in pitch but also in intensity, than any of the other sounds. It is not difficult to show that these sound fluctuations are dependent upon cardio-vascular changes; for the particular compression pulses in which they occur are distinguished from all others by their configuration, being broader across the top. Furthermore, they usually are the shortest pulses in duration, or follow immediately upon the shortest pulses. In the absence of simultaneous blood pressure records it is impossible to determine the exact nature of the cardio-vascular phenomena here transpiring. For present purposes, however, we are alone interested in the fact that, whatever, may be its nature, a cardio-vascular phenomenon that alters the intensity of water hammer action also alters the intensity and the pitch of the compression sounds in the same direction.

Configuration of the peripheral pulse

The configuration of the peripheral pulse also throws some light upon the nature of the process that produces the sounds. In the present experiments the pulse, it will be recalled, was recorded by letting the artery rest upon the head of a special receiving tambour in the floor of the stethoscope. This method, while not a particularly delicate or constant one, was employed, firstly, because it did not necessitate applying any pressure to the artery and, secondly, because it was desirable to obtain the pulse as close to the compression chamber as possible. Often it was not delicate enough to record the first pulses that came through. In the case of the particular record used here for purposes of illustration (fig. 1) it did actually record the very first pulse that gave rise to a sound.

The first pulses that come through, as has been said, usually give no evidences of sound vibrations, they merely produce small, rounded elevations. When, however, the sound waves become visible, or, at least, shortly thereafter, the level of the record is raised a short distance with the first sound wave. This abrupt rise is followed by a slight decline to a second gradual rise which attains a greater height than the first. Both of these elevations gain in amplitude with decompression, the first, however, more rapidly than the second, with the result that when the third phase sounds are reached the first fully developed sound wave may attain a greater height than the second rounded elevation and it attains this height in the extraordinarily brief period of one-half of a double sound vibration, or approximately 0.002 second. With the onset of the fourth phase sounds the first rise begins to diminish in amplitude while the second elevation continues to gradually increase until with a further fall of compressing pressure, usually of some 5 to 10 mm. of mercury, the pulse has taken on the appearance of a normal wave.

There can be no doubt but that the abrupt rise of the pulse during the loudest sound phases is the result of an impact that is extremely sudden and much more forcible than any the pulse wave of itself delivers, for it may rise to a greater amplitude than the pulse proper. The entrance of the blood under practically systolic pressure into an empty artery in which the pressure may be zero, which is Ehret's explanation of the Korotkoff sounds, fails to account for this rise of pressure above the level of the aftercoming pulse. It might, however, be maintained that the low, rounded waves that come through in asso-

ciation with the first phase sounds could not come from an impact that is sharp enough to produce a sound. This objection loses much of its force when it is recalled that the quantity of blood that succeeds in getting through the compressed artery at this stage is very small indeed. While it may be sufficient to so distend the artery at the point of impact as to produce a sound, it nevertheless may not be sufficient to propagate a sharp pulse for any considerable distance along the relatively empty artery.

Effects of occlusion of the artery on sound production

When one occludes the artery some distance below the stethoscope in such a way as to leave the artery distended with blood and then observes the sounds in the usual manner while the compressing pressure is falling, the sequence and character of the sounds seem to be but little altered from those heard when the artery is open, except that the murmur of the second phase sounds is lacking. This observation again demonstrates that for the production of the arterial compression sounds in all of their phases, excepting the murmurs, an empty distal artery is not an essential condition.

Occlusion of the artery may however alter the loudness and quality of the sounds. These effects are best brought out by lowering the compressing pressure in steps and noting at each step the intensity and character of the sounds, first while the artery is open, and then while it is occluded. The artery in such experiments must be so occluded as not to alter its position in the stethoscope or arteriograph, and precautions must be taken to avoid such effects upon the quality and loudness of the sounds as might result from variations in the size of the cleft where the artery passes through the aperture of the stethoscope. The former requirement is met by employing the well-known method of looping a thread around the artery and occluding the artery by drawing the ends of the thread through a glass tube held rigidly in place and so that its orifice just touches the artery. And the latter requirement is met either by filling the cleft with vaseline or by leaving open the side tube of the stethoscope. It might be added, however, that excepting some loss of sound the condition of the side tube, whether open or closed, has been without material effect.

The results obtained in four typical experiments are here given in tabular form (Table III). It will be seen that the changes wrought in the sounds by occlusion of the artery are by no means constant. It is nevertheless possible to recognize certain more or less constant effects:

TABLE III

Showing the modification of sound by occlusion

PHASE	EXPERIMENT 7	EXPERIMENT 9	EXPERIMENT 16	EXPERIMENT 17	EXPERIMENT 20
Early first	Slightly louder, duller	Disappears	No change, or increases first and then disappears	Fainter and disappears	Duller and very faint
Late first	Fainter and duller		Duller, lower pitch, slightly fainter, or slightly higher pitch, then fainter		Fainter
Second	Fainter and duller	Feebler and duller	Same as late first	Murmur disappears, sounds become very faint and duller; later not so faint	Duller and fainter, murmur disappears
Early third	No change in intensity, duller		Same as late first	Remain loud but become dull	Duller and fainter
Late third	Duller and slightly lower pitch, intensity same or louder	Snapping quality almost disappears, intensity diminishes	Same as late first	Little change in intensity or quality	Changed but slightly, perhaps slightly higher
Early fourth	Louder and duller	Duller, no change in intensity	Clearer, slightly higher, no change in intensity		Very slight change
Late fourth	Slightly louder and more pistol-shot	No change in intensity, higher in pitch	Higher pitch and slightly louder	Slightly louder and higher	Very slight change
No compression	Louder and duller	Louder, no change in character			Very slight change

Early first phase: The sounds become fainter and disappear; occasionally they first increase in intensity and then become fainter.

Late first phase: The sounds become fainter.

Second phase: The murmur disappears and the sounds become fainter.

Early third phase: The sounds either become slightly fainter or suffer no change in intensity.

Late third phase: Changes in intensity, if present, are slight, and then it either increases or decreases.

Early fourth phase: The sounds either do not change or increase slightly in intensity.

Late fourth phase: The intensity of the sounds is usually increased.

Zero compression: The intensity of sounds is always increased.

In an effort to ascertain the factors actually at work in producing these alterations in the intensity of the sounds we will analyze a record of the pressure changes in the compression chamber obtained in one of these occlusion experiments. It is seen in Table IV that during the first and early second phases occlusion elevates the base line (slight rise of compressing pressure), reduces the amplitude of the oscillations (extension upward of the lower cone and rise of compressing pressure), and increases the amplitude of the peripheral pulse (reflection of the pulse wave). At this stage of the experiment undoubtedly only a very small quantity of blood succeeds in traversing the compression chamber with each pulse. The impact therefore could not extend very far from the point where it strikes; and as the artery fills, the point of impact would be carried away from the stethoscope. This and the enfeeblement of sound that would be associated with a rise of the compressing pressure, might suffice to account for the diminution in the intensity of the sounds usually noted. At the same time it is conceivable that occlusion of the artery might increase perceptibly the force of water hammer and might facilitate the transmission of the impact that causes the sound (see below). Both of these factors might act to increase the intensity of the sounds, at least until the point of their origin had receded some distance from the stethoscope. Under these circumstances the sounds might at first increase in intensity and then decrease, as actually happens in a certain number of the cases (Table III, experiment 16).

In the late second phase occlusion for the first time alters materially the configuration of the compression pulse. The alterations are as follows (See Table IV):

TABLE IV

Analysis of a record (Experimental 17) showing the effect of occluding the artery peripherally.

PHASE	ELEVATION OF BASE LINE UPON OCCLUSION	AMPLITUDE FIRST CREST				TIME TO FIRST CREST		TOTAL AMPLITUDE				TIME ELAPSING BETWEEN FIRST AND SECOND CRESTS		AMPLITUDE FIRST TO SECOND CREST		SOUND CHANGES
		Open		Closed		Open	Closed	Open		Closed		Open	Closed	Open	Closed	
		Ave.	Range	Ave.	Range			Ave.	Range	Ave.	Range					
	mm.	*mm.*	*mm.*	*mm.*	*mm.*	*sec.*	*sec.*	*mm.*	*mm.*	*mm.*	*mm.*	*sec.*	*sec.*	*mm.*	*mm.*	
First	3−							8.1	7.0–9.0	7.8	6.7–9.0					Fainter
Early second	3−							11.5	10.8–12.0	10.9	10.0–11.5					Fainter
Late second	3−	12.1	12.0–13.5	9.8	9.5–10.0	0.042–0.05	0.032–0.042	14.5	14.2–14.8	14.8	14.5–15.0			2.4*	5.0*	Remain fairly loud
Third	3+	12.1	11.5–12.5	10.6	10.0–11.2	0.03	0.03	15.0	14.0–15.5	15.2	14.5–16.0	0.050	0.022	3.1	4.6	Remain loud
Last third to early fourth	3++	8.6	8.0–9.7	6.9	5.5–8.5	0.03	0.024–0.023	11.6	11.0–12.0	11.1	10.0–12.7	0.072	0.022	3.0	4.2	Little change in intensity or quality
Fourth	1	4.8	4.4–5.0	5.0	4.8–5.2	0.02	0.02–0.022	7.5	7.0–8.0	8.6	8.0–9.0	0.065	0.018	2.7	3.6	Slightly louder

* First crest not very clear.

(a) The amplitude of the first crest is lowered from 12.2 to 9.8 mm. (b) The time to the first crest is reduced from about 0.043 to 0.037 second. (c) The amplitude subtended by the first and second crests is increased from 2.4 to 5.0 mm. (d) The total amplitude is increased very slightly—from 14.5 to 14.8 mm. If we take the ratio of the amplitude of the first crest to the time it is attained as a rough index to water hammer action, we have evidence in the foregoing figures that occlusion reduces slightly the force of the water hammer. We can understand, therefore, why, upon occlusion, the sounds, though fainter, "remain fairly loud."

While the third phase is at its height the effects of occlusion upon the configuration of the compression pulse are similar to those just described: (a) The amplitude of the first crest is lowered slightly,—from 12.1 to 10.6 mm. (b) The time to the first crest is not perceptibly altered; it is in the vicinity of 0.02 second under both conditions. (c) The amplitude subtended by the first and second crests is increased from 3.1 to 4.6 mm. (d) Now the second crest is attained very much more quickly while the artery is occluded—0.022, as compared with 0.05 second. The second rise, which is due to the accumulation of blood in the occluded artery, is therefore almost as steep as the first. (e) The total amplitude again remains practically unchanged—15 mm. while open and 15.2 mm. while closed. Consequently, for reasons given with the preceding set of conditions, it seems obvious, on the basis of water hammer, that the sounds should "remain loud" when the artery is occluded.

The changes noted upon occluding the artery when the sounds are in the vicinity of the limit between the third and fourth phases are as follows: (a) The amplitude of the first crest is lowered from 8.6 to 6.9 mm. (b) The time to the first crest is reduced from 0.03 to 0.023 second. (c) The amplitude subtended by the first and second crests is increased from 4 to 4.2 mm. (d) The second crest is attained more quickly—0.022 second as compared with 0.072 second. (e) The total amplitude is very slightly reduced—from 11.6 to 11.1 mm. Here the sounds are changed but little in intensity or quality. The figures would seem to indicate that water hammer action is slightly increased; and inasmuch as the sounds are already dull, little change in their quality is to be expected.

When the sounds are well along in the fourth phase the following changes in the configuration of the compression pulse are to be noted: (a) The amplitude of the first crest, which is now not clearly indicated,

is not especially changed—5 mm. as compared with 4.8 mm. (b) Neither does the time to the first crest change appreciably; (c) but the amplitude subtended by the first and second crests, considering the total amplitude, is decidedly increased—from 2.7 mm. to 3.6 mm.; (d) while the second crest is attained very much more rapidly—0.018 second as compared with 0.065 second; (e) and the increase in total amplitude is now relatively the greatest of the whole series—8.6 from 7.5 mm. It would therefore seem that in this part of the experiment water hammer, as indicated by the amplitude and steepness of the first rise, is not altered.[5] On the other hand, the distention caused by the second rise when the artery is occluded now assumes a position of considerable importance relatively: although it is not quite so high as, it now reaches its crest in less time than, the first rise. Its tendency to set the arterial walls into vibration would therefore be quite as marked as that of the first rise. Inasmuch, therefore, as the first rise is not materially altered by occlusion of the artery whereas the second rise then practically comes into being, it is easy to comprehend why the sounds become "slightly louder upon occlusion."

A hurried analysis of this record therefore shows that the changes in sound caused by the occlusion of the artery in this particular experiment are explicable on the basis of water hammer action when due allowance is made for the effects of such accessory changes as the extension of the lower cone, the distention of the peripheral artery by the pulsatile entrance of the blood, and changes in the compressing pressure. We do not happen to have made any record of an experiment, such as No. 7, Table III, in which occlusion of the artery in the third phase caused the sounds to increase in intensity. It is therefore impossible to determine whether such an increase is due to an increase of water hammer action or of some other factor. We have as yet no explanation to offer with regard to the cause of the dulling of the sounds so often noted in these occlusion experiments.

[5] This, it might be noted, is an interesting confirmation of our assumption that the first crest is the result of water hammer; for at this stage of the experiment there is no reason why occlusion of the artery should alter materially any of the factors that participate in water hammer: the lower artery is already fairly full, the lower cone is practically eliminated, and the compressed segment now alters its capacity only through the filling permitted by the elasticity of the arterial wall.

Location of the loudest and the characteristic sounds

In the dog the sounds, when loud, can be heard with the phonendoscope over the artery above the compression chamber (of this more later) and over the upper and lower ends of the compression chamber. It is interesting, however, that these sounds usually differ somewhat from those heard over the lower artery in being somewhat blowing, or at least, duller, in character; the characteristic snap usually is first clearly heard at the point where the artery leaves the arteriograph.

The distance along the distal artery the characteristic sounds can be heard with the stethoscope depends somewhat upon the sound phase. In the early first phase the sounds are heard best close to the compression chamber; at a distance of one or two centimeters they usually can no longer be heard. In the second phase the sounds are transmitted with diminishing intensity a considerable distance down the artery, though the murmurish quality may not be heard beyond 4 cm. During the later phases the sounds are very well transmitted; they diminish slightly with the distance, but can be well heard along the whole course of the freed artery. During the first phase, when the sound is clearly audible close to the arteriograph but not at a distance, it is found that upon occluding the artery distally the sound, though fainter, may become almost equally audible along the entire length of the distended artery.

Essentially similar results are obtainable in man when the sounds are examined over the armlet and at different distances below it. In these observations, we have used a Riva Rocci tube 4 cm. wide, because of all of the armlets now in use this is composed of the fewest layers of material; the button of the phonendoscope resting on it is separated from the underlying tissues by two thin layers of cloth-covered rubber only. Sounds can be heard through this armlet along the course of the brachial artery but they are distinctly fainter over the upper than the lower half of the tube (20). In the arm below the tube the sounds are loudest at the lower edge of the band and their intensity diminishes along the course of the artery though they can be heard for a considerable distance (20). It is scarcely possible to duplicate the observations on the effects of occluding the artery because in man, on account of the simultaneous compression of the veins, the arteries are distended to a certain extent in all parts of the observation.

These results leave little room for doubting that the characteristic Korotkoff sounds start at the lower end of the compressed segment of

artery; that they are transmitted from this point along the course of the artery; and that they are transmitted for a longer distance along a full than along an empty artery. The latter fact furnishes additional evidence for the view that the sound is developed along the artery by the transmission of a wave. This wave would not be well transmitted when it is started through an empty artery by a small volume of blood. Distending the artery would, however, and does, increase its ability to transmit shocks.

Location of sensation

As is well known the subject of a blood pressure estimation experiences in his arm a sensation resembling a rather sharp shock as long as the compressing pressure lies in the systolic-diastolic region. At all other compressing pressures the pulsatile sensation is not that of a shock. Now that evidence has been obtained indicating that the physical basis of the process enacted under the armlet is water hammer, any one who has felt this shock will recognize the resemblance of the sensation to that which one would expect water hammer to exert.

In my own experience the shock has always been most distinctly felt under the lower part of the armlet (20) where the impact of the water hammer must take place. In order, however, to test this matter in a wholly unbiased way, we have had several good subjects for this purpose, who were unfamiliar with the object of the tests, point continually with the finger to the spot where the sensation was most distinct while blood pressure estimations were being made on them by the method of continuous escapement. In each case the shock was located under the lower edge of the armlet and in most instances at a point that corresponded with the lower 1 or 2 cm. of the pneumatic bag. In all probability this is about the level at which the artery begins to open out from beneath the compression.

Sounds heard central to the compression

It has been maintained that because in man the Korotkoff sounds cannot be heard above the armlet they therefore cannot be produced by any process taking place under the cuff itself (4). Even if this were true it would not preclude the possibility that sounds originate in a process enacted at the lower edge of the armlet. But as a matter of fact sounds can be heard in the artery above the cuff (21).

We have not investigated this question systematically; indeed ob-

servations have been made on only two subjects. Both were normal young men with blood pressures that might be regarded as at the upper limit of normal and with normal compression sounds. They were selected for these observations because they had long thin arms. The armlet was first fastened to the arm in the usual position and the artery ausculted with the phonendoscope in the bend of the elbow. Then the armlet was shifted to a lower position and the artery ausculted centrally in its most superficial position between the biceps and triceps muscles. The results obtained in both cases were essentially alike; we will therefore describe only one set.

Listening below the cuff, the first sounds were heard at 128 mm. Hg; they became duller at 90 mm. and disappeared at from 85 to 75 mm. Listening above, no sound was audible when the arm was uncompressed. At 160 mm. Hg, however, that is, well above systolic pressure, a sound could be heard. This sound became perceptibly fainter at 124 mm. Hg and at the same time a second sound following the one first heard became audible. The interval between these two sounds diminished as the compression decreased until at about 90 mm. Hg it was no longer possible to distinguish between them; and soon thereafter no sound could be heard at all. It should be added that the sound audible above the armlet when the artery is occluded by a pressure in excess of the systolic pressure does not owe its origin to any property peculiar to the armlet; for the same sound is obtained when the artery is occluded by the finger.

In the dog it is difficult to find room for the stethoscope above the compression chamber and still have a large enough artery in the arteriograph to yield good sounds. But when the phonendoscope is placed on the distal artery a sound, probably emanating from the uncompressed artery above, can be heard even when the compressing pressure exceeds the systolic pressure. As in the case of man a second sound becomes audible at lower compressing pressures. When first heard this second sound is well separated from the first and has the characteristics of the pistol shot sound. As the compressing pressure falls the second sound goes through the five phases, while the first sound steadily grows fainter and approaches closer and closer to the second, until the two merge.

In both man and the dog the first of the two sounds described above is probably developed or enhanced, as the case may be, by the added energy the pulse delivers to the artery when it is occluded. In man it is picked up directly from the upper artery by the phonendoscope; in

the dog it is transmitted as sound to the phonendoscope below. On the other hand in man the second sound is transmitted upward perhaps partly as sound, though it is conceivable that it is also developed locally by the retrograde impact of water hammer, while in the dog it is in the main developed locally by the transmitted impact. The fact that they merge as the compressing pressure falls is in keeping with the observation that the Korotkoff sounds under similar circumstances appear earlier and earlier in the pulse cycle.

Behavior of the central and peripheral arterial pressures during decompression

It has been shown that the Korotkoff sounds are a manifestation of water hammer; we should therefore expect the arterial pressures central and peripheral of the compression chamber to manifest the changes characteristic of water hammer.

Peripheral pressure. Presumptive evidence has already been presented indicating the existence of peripheral pressure effects consistent with the premises: while loud sounds are in evidence the initial rise of the peripheral pulse may be higher than the crest proper of the pulse. Direct proof of the existence of the peripheral pressure effects of water hammer has been obtained in an experiment in which the artery was cut below the stethoscope and the central stump connected with a mercury manometer through a stopcock which in one position permitted of the free transmission of the pressure and in another position acted as a maximum valve (22). It should be added that, through an oversight, the valve was not delicate enough to give the best results. The results obtained can therefore be regarded as only qualitatively correct; they, however, suffice for present purposes. The experiment shows conclusively (8 estimations) that while those sounds are audible that are well transmitted along the course of the artery, namely, the third phase sounds and possibly the late second phase sounds also, the maximum pressure is higher by from 8 to 18 mm. Hg than the maximum end pressure of the uncompressed artery. During the fourth phase the maximum pressure is not so high as during the third.

Central pressure. The water hammer effect is produced in the compression chamber by the entrance of blood into the opening artery with a speed that exceeds the normal rate of flow. But blood cannot be furnished from above at a velocity greater than the normal with-

out causing some fall of pressure centrally. We would therefore expect the central pressures to fall momentarily in each pulse while the water hammer is acting, and since the velocity of flow is the main factor that determines the force of the water hammer, we would further expect this fall of the central pressures to vary with the intensity of the sounds. Whether or not this occurs in animals we have not determined. It, or something analogous to it, does, however, occur under similar conditions in a circulation schema. In this connection we quote from an article published by the author in 1904 (14, p. 75).

. . . . With each diminution of the outside (*compressing*[6]) pressure, with its consequent increase in the velocity of blood flow, the *central* pressure in the schema falls slightly. But we find that as we approach the pressure at which maximum pulsations are obtained, this diminution in the minimum (and maximum) pressure is accelerated,[7] but that the pressure recovers when the amplitude of the *compression* pulsations begins to diminish, and that it then continues to fall off gradually. This accelerated diminution of the minimum (and maximum) pressure is quite independent of variations in the rate of *peripheral* flow and has not as yet received a satisfactory explanation.

This result, then impossible of explanation, now is readily accounted for. Indeed it is a necessary manifestation of water hammer as produced by the methods employed in the estimation of blood pressure. It will be noted that it manifests itself in the circulation schema when the compressing pressures lie between those that determine the critical increase and decrease in the amplitude of compression oscillations, which mark respectively the systolic and the diastolic pressures.

SUMMARY

The more important observations and conclusions of this investigation may be summarized as follows:

The Korotkoff sounds are produced by water hammer.

1. The evidence in favor of this conclusion is as follows:

a. While sounds are in evidence, blood enters the compressed artery with a velocity far in excess of the normal.

b. When the sounds are loud (third phase) the artery in the compression chamber can be made to act as a hydraulic ram through the peripheral artery.

[6] Italicized words are added in order to make the context clear.

[7] As a matter of fact the acceleration begins during decompression with the first abrupt increase in amplitude of the compression pulse (see Table III and fig. 12 of the article referred to (14) for further details).

c. The pressures central of the compressed artery (circulation schema) fall while the wider compression oscillations are recording.

d. The configuration of the compression pulse conforms with the requirements of the water hammer hypothesis.

e. The sounds are located in that phase of the pulse cycle in which a water hammer would strike.

f. The intensity of the sounds varies during decompression as the values, obtained from records, assumed to indicate the force of the water hammer.

g. Calculation locates the initial site of sound production in the lower end of the compression chamber.

h. That the sound is produced by a sudden impact is indicated by the fact that the first of the series of vibrations associated with each sound is the highest.

i. The form of the pulse beyond the compression chamber is such, in certain stages at least, as could be produced only by a sudden impact more forcible than any the pulse itself could strike.

j. The sounds are loudest at the lower edge of the compression chamber.

k. The sensation perceived in the arm during the systolic-diastolic phase of decompression is localized where water hammer would strike and has the characteristics of a blow delivered by water hammer.

2. The main objections to other views on the origin of the Korotkoff sounds are as follows:

a. The fact that the Korotkoff sounds can still be obtained when the artery is occluded at the lower orifice of the compression chamber and when the artery below the compression chamber is distended with blood renders untenable views based on the presence of an empty peripheral artery (3).

b. Views assigning prime significance to the tissues surrounding the artery (6) are invalidated by the fact that the bare artery suffices for the production of characteristic sounds.

c. Resonance of the air chamber (8) is shown to be unessential for the production of characteristic and loud sounds. The evidence presented in support of this view is shown to be open to a wholly different interpretation, namely, limitation of the movements of the walls of the compressed artery.

d. The view ascribing the sounds solely to changes in the form of the tube in the compression chamber (5) is based upon a wrong conception of the sequence of these changes in form. Furthermore, it is shown

that the artery below the compression chamber during certain of the sound phases contributes to sound production.

3. The mechanism of sound production, in a word, is that the water hammer moving through the artery in the compression chamber, under usual circumstances, strikes the stagnant blood in the uncompressed artery below and distends the artery there so as to give rise to sound. The wave started by this impact is transmitted down (and up?) the artery with sufficient amplitude to produce sound locally as it proceeds, but only when the volume of blood coming through is sufficient and when the lower artery already is fairly full of blood, and therefore ordinarily only in the late second and third sound phases.

BIBLIOGRAPHY

(1) Erlanger: This Journal, 1916, xxxix, 401.
(2) Friedreich: Ref., Fischer, Deut. Med. Wochensch., 1908, xxxiv, 1141.
(3) Korotkoff: Ref., Gittings, Arch. of Int. Med., 1910, vi, 196, and Howell and Goodman: Univ. of Penn. Med. Bull., 1910, xxiii, 470.
(4) Ehret: Münch. Med. Wochenschr., 1909, lvi, 959.
(5) MacWilliam and Melvin: Heart, 1914, v, 153.
(6) Flack, Hill and McQueen: Proc. Roy. Soc., B, 1915, lxxxviii, 508 and 516.
(7) von Frey: Ref. Neu, Inaug. Diss., Heidb., 1902.
(8) Gittings: Arch. of Int. Med., 1910, vi, 196.
(9) Russell: Textb. on Hydraulics, N. Y., 1913, 176.
(10) Joukowsky: Ann. Imp. Acad. Sci. of Petrograd, ix, 5, Ref., Harza, Bull. Univ. Wisc., Eng. Series, 1908, iv, 152.
(11) Tigerstedt: Erg. d. Physiol., 1909, vii, 620.
(12) Grünmach: Arch. d. Physiol., 1888, 137.
(13) Hewlett and van Zwaluwenburg: Heart, 1909, i, 87.
(14) Erlanger: Johns Hopkins Hosp. Rep., 1904, xii, 53.
(15) Warfield: Arch. of Int. Med., 1912, x, 258.
(16) Hooker and Southworth: Arch. of Int. Med., 1914, xii, 384.
(17) Lang and Manswetowa: Deut. Arch. f. Klin. Med., 1908, xciv, 441.
(18) MacWilliam and Melvin: Proc. Physiol. Soc., Mch. 14, Journ. of Physiol., 1914, xlviii.
(19) Sahli: Lehrbuch d. klinische Untersuchungsmethoden, 1909, 5th ed., 377.
(20) Schrumpf and Zabel: Münch. Med. Wochenschr., 1909, lvi, 704.
(21) Fischer: ref. (20).
(22) Gesell: This Journal, 1916, xxxix, 239.

PROCEEDINGS OF THE AMERICAN PHYSIOLOGICAL SOCIETY

Twenty-Eighth Annual Meeting

Boston, December 27, 28 and 29, 1915

Food accessories. T. B. Osborne and L. B. Mendel.

Food accessories. E. V. McCollum.

Food accessories. Carl Voegtlin.

The formation and structure of the fibringel. W. H. Howell.

Experiments on the mechanism of osmosis. Jacques Loeb.

Further observations on over-activity of the cervical sympathetic. W. B. Cannon and Reginald Fitz.

In an animal with rapid heart, falling hair, increased excitability, and a steadily mounting metabolism, which had reached about 60 per cent above the average—all these symptoms resulting from union of the phrenic nerve to the cervical sympathetic trunk—removal of the thyroid gland on the operated side stopped the progress of the disease and brought the metabolism down within normal limits. Whereas other animals with the disease had died within three months of the first appearance of the symptoms, this animal lived normally for seven months after the operation, and was then purposely killed.

Some new observations on the uric acid content of the blood. Otto Folin and R. D. Bell (by invitation), with the assistance of G. Le B. Foster.

On continuous insufflation through the humerus in fowls. A. L. Meyer and S. J. Meltzer.

In fowls the bones are connected with the air sacs and lungs. In our experiments a continuous current of air was insufflated through the humeri in chickens; in most experiments the air escaped through a tracheal cannula. The continuous insufflation was made under various air pressures and the duration varied from a few seconds to more than two hours. The insufflation was made either with pure air or air admixed with ether or with carbon dioxide. We shall report here only a few of the facts which were observed in these experiments.

When the insufflation pressure was about 10 mm. of mercury, all respiratory oscillations disappeared; the thorax stood still in a more

or less exaggerated state of inspiration. The degree of pressure, required to produce such a stand-still apparently varied with the size and perhaps also with the vigor of the animal. Fifteen millimeters never failed to produce a stand-still. On the interruption of the insufflation in most of the experiments the thorax immediately assumed an expiratory state in which it continued to stand still variously from a few seconds to half a minute and longer. Following this, inspiratory oscillations set in which very gradually resumed their former depth. Ether invariably prolonged the state of the expiratory after-effect. In a few instances, a stand-still in a reduced inspiratory state preceded the expiratory after-effect. The inspiratory stand-still during insufflation was soon interrupted by some moderate oscillations, when CO_2 was added to the insufflated air. Insufflation of air containing 3 per cent of CO_2 or more does not bring on a stand-still; on the contrary, it increases the inspiratory and expiratory amplitudes of the respiration.

The prolonged continuous insufflation, practiced in these animals, is surely capable of removing a good deal of CO_2 from the body, much more so than in any form of rhythmical artificial respiration or in forced respiration. Nevertheless, in no instance did a symptom make its appearance during or after the insufflation which could be interpreted as "shock." Furthermore, the line indicating the expiratory stand-still ran along the peaks of the expiratory oscillations, and some times even above them. In fowls the expiration is even normally of an active character. The apnoea, then, which follows prolonged insufflation means a tetanic contraction of the expiratory muscles. Our experiments, therefore, demonstrate the fact that the apnoea vera which follows continuous insufflation does not consist in a passive state of the thorax, but rather in the production of a tetanic state of the respiratory muscles, chiefly those of expiration. Since the continuous insufflation in our experiments means a considerable reduction in the content of CO_2 of the body, or as it is now called, acapnia, it follows that in our experiments the acapnia had a stimulating effect upon the respiratory musles and not as it is usually assumed that the lowering of the CO_2 means the reduction or abolition of a stimulus. On the other hand, the experiments in which CO_2 was added to the insufflated air, the respiratory rhythm was started or the unsuppressed rhythmical oscillations were augmented. In other words, our experiments seem to show that the reduction of CO_2 acts as a stimulus apt to produce a tetanus of the respiratory muscles, while the increase of CO_2 favors the augmentation of the respiratory rhythm.

The influence of the adrenals on the kidneys. E. K. Marshall and D. M. Davis (by invitation).

Heredity and internal secretion in the origin of cancer in mice. Leo Loeb.

Different strains of mice kept in the same environment differ very much in the frequency with which cancer occurs among them. In succeeding generations the percentage figure for cancer is fairly constant

in different strains of mice. Equally characteristic for different strains is the age at which cancer occurs. Hybridization experiments confirm and extend these conclusions. In our experiments the tendency to cancer was not in the majority of cases a recessive character.

These data are a prerequisite for further studies of factors responsible for the spontaneous development of cancer as well as for attempts to find a rational basis for diminishing the frequency of cancer.

In former investigations we found that a combination of a mechanical stimulus and the influence of a substance secreted by the corpus luteum led to the production of rapidly growing tumor like newformations, the deciduomata. These facts as well as the significance of the corpus luteum for the growth of the mammary gland suggested a possible importance of the corpus luteum for the spontaneous development of cancer in mice. We found that castration of mice at or below the age of six months (corresponding to a period of life, when the animals are already sexually mature) diminished the cancer incidence in a very pronounced way: the cancer rate fell from 60 or 70 per cent in normal mice to 9 per cent in castrated mice.

Non-breeding mice with functioning ovaries develop cancer in a somewhat smaller percentage of cases and at a somewhat higher age than normal breeding mice. The influence of prevention of breeding is much less marked than castration, a finding in accordance with the fact that, while castration eliminates the effect of the corpora lutea, non-breeding merely diminishes or modifies it. Non-breeding may also diminish mechanical irritation of the mammary glands. It appears probable that with the coöperation of hereditary factors all those internal secretions are factors in the origin of cancer which initiate or sustain continuous or periodic growth processes.

The effect of X-rays on cancer immunity. JAMES B. MURPHY.

The presence of posterior lobe secretion in the cerebro-spinal fluid. HARVEY CUSHING and GILBERT HORRAX (by invitation).

The influence of gastrectomy on subsequent pancreatectomy in dogs. J. R. MURLIN and J. E. SWEET.

In 1913 Murlin and Kramer[1] reported the observations that sodium carbonate reduces the output of sugar in the urine of depancreatized dogs and hydrochloric acid increases it. Since the pancreas produces sodium carbonate in proportion to the hydrochloric acid produced by the stomach (Pawlow, Cohnheim and Klee) these observations suggested the possibility that the consequences of pancreatectomy may be due in part to the unneutralized HCl of the stomach. This view was presented in brief in November 1913.[2] Two dogs, in which the stomach contents were excluded from the intestine by a band placed

[1] Journal of Biological Chemistry, 1913, xv, 365.

[2] Murlin: Postgraduate, N. Y., 1913, November number.

about the pylorus at the time of pancreatectomy, developed no glycosuria for twenty-four hours. Dr. Kramer assisted with these operations.

A third dog whose stomach was removed in the same operation as the pancreas, by Dr. J. A. Hartwell, developed no glycosuria for thirty-six hours and then for two more days showed a D: N ratio below 1. A fourth dog, also operated by Dr. Hartwell, the pancreas being removed one week after the stomach was removed, gave no sugar in the

Dog VIII. Gastrectomy November 11; Pancreatectomy, December 9, 1915

WEIGHT	DATE	TIME	URINE			CO_2	O_2	R. Q.	FOOD AND REMARKS
			TOTAL D	TOTAL N	D: N				
						L. per hr.	*L. per hr.*		
7.05	Dec. 10	9.10 *a.m.*	2.50	2.16	1.11				Given milk by mistake
6.90	11	9.35	0.305	0.496	0.65				
		10.17-11.17				2.434	3.453	0.73	
		11.17-12.17				2.511	3.331	0.75	
		12.35	0.244	0.40	0.61				50 gm. glucose by tube 20 gm. glucose subcutaneous
		3.45- 4.46				3.120	4.030	0.77	
		5.15- 6.15				3.039	4.000	0.76	
		6.15- 7.15				3.149	4.316	0.73	
	12								200 cc. milk
6.05	13	3.42- 4.42				2.817	3.921	0.72	No food
		4.42- 5.42				3.596	4.948	0.73	
6.05	14	11.15	0.0						
6.05	15	4.35	0.0						
		4.58- 5.58				2.413	3.408	0.71	
		5.58- 6.58				2.465	3.427	0.72	8.00 *p.m.* fed 30 grams starch c̄ digestive powder
		7.35	0.0	0.378					
6.15	16	9.00 *a.m*	2.84						
		12.20	0.0						1.10 *p.m.* fed 50 grams cracker meal c̄ dog's pancreas
		3.25- 4.25				3.654	4.994	0.73	
		4.25- 5.25				2.873	3.998	0.72	

urine within twenty-four hours, and exhibited the D: N ratio of 1 or thereabouts for two days. All of these dogs died by accident. Only one of them had a temperature above normal following operation.

In June, 1914, one of us (S.) removed the stomach from a dog and eleven days later removed the pancreas. The urine following the second operation was analyzed daily by Dr. H. B. Lewis in Dr. Taylor's laboratory. For about thirty-six hours it contained no sugar then for fourteen days more exhibited a D: N ratio varying from 0.7 to 1.7.

More recently the stomachs have been successfully removed from three dogs and one of these has also been deprived of the pancreas four weeks after gastrectomy. Observations on this dog for the first week following the second operation are recorded in the table.

It will be seen that the dog again starts off with the ratio of 1.1. Notwithstanding that milk was given by mistake on the first day, the D: N on the second day was only 0.61. The R. Q. on this day shows that the dog could burn some glucose. The fourth day was a fasting day and on the fifth the urine contained no sugar. This dog at the present writing (December 23) is still alive and is sugar free when not fed. Up to the end of the first week (December 15) the R. Q. shows that the dog was still capable of oxidizing some ingested sugar.

The distribution of suprarenin-yielding tissue in different animals. M. E. Fulk (by invitation) and J. J. R. MacLeod.

The action of minimal doses of adrenalin. Walter J. Meek.

The effects of suprarenal feeding on the white rat. R. G. Hoskins and Augusta D. Hoskins (by invitation).

Adrenalin content of the blood in conditions of low blood pressure and "shock." E. A. Bedford (by invitation) and H. C. Jackson. Read by title.

Rhythmical changes in the resistance of dividing sea-urchin eggs to hypotonic sea-water. Ralph S. Lillie.

In dilute sea-water (*e.g.*, 60 volumes tap-water *plus* 40 volumes sea-water) fertilized sea-urchin eggs (Arbacia) take up water osmotically and swell. A medium of this composition does not, however, cause cytolysis (loss of pigment and disintegration) unless the eggs are introduced at or near the time of appearance of the cleavage furrow. This change is associated with a marked decline in the resistance of the eggs to hypotonic media, and cytolysis is then rapid and complete. When the cleavage-furrow is fully formed the original resistance rapidly returns. A similar reversible decline of resistance accompanies the second and third cleavage.

The following record of an experiment will illustrate. Eggs were placed in hypotonic sea-water at different intervals after fertilization. (Up to forty minutes no change takes place beyond swelling.)

TIME AFTER FERTILIZATION AND CONDITION OF EGGS WHEN PLACED IN SOLUTION	PROPORTION OF EGGS CYTOLYZED AFTER 30 M. IN DILUTE SEA-WATER
40 m.	Nearly all eggs intact; 1–2 per cent cytolyzed
42 m.	4–5 per cent cytolyzed
44 m.	*ca.* 10 per cent cytolyzed
46 m. (no furrow visible)	*ca.* one-third (35–45 per cent)
48 m. (furrow beginning in a few eggs)	80–85 per cent cytolyzed
50 m. (furrow in *ca.* half the eggs)	90 per cent or more cytolyzed
52 m. (nearly all eggs cleaving)	95 per cent or more cytolyzed
54 m. (most eggs in 2-cell)	60–70 per cent cytolyzed
56 m. (cleavage complete in nearly all)	25–35 per cent cytolyzed
58 m. (all in 2-cell stage)	*ca.* 20 per cent cytolyzed
60 m. (all in 2-cell stage)	*ca.* 10–15 per cent cytolyzed
62 m. (all in 2-cell stage)	Few cytolyzed (*ca.* 5 per cent)

The minimum of resistance is found *during the formation of the furrow.* Both the decline and the return of resistance are rapid, the greater part of each phase occupying four or five minutes. Evidently the plasma-membrane becomes much less resistant to disruption at the time of cleavage; *i.e.*, its coherence or extensibility is decreased; with this change is probably associated an increase of permeability and a decrease of electrical polarization. A definite change in the physical properties of the membrane is thus associated with division of the cell-body; increased surface-tension, resulting from decreased electrical polarization, is probably the chief factor conditioning the change of form.

Mass-action in the activation effect of butyric acid on unfertilized starfish eggs. RALPH S. LILLIE.

Simple exposure to solutions of butyric acid (in sea-water or van't Hoff's solution) is sufficient to induce complete activation in unfertilized starfish eggs, provided the proper time of exposure is employed. With too brief exposures activation is partial (membrane-formation followed by breakdown in early development); over-exposure injures the eggs and prevents development. The activation of under-exposed eggs may be completed by a second exposure to butyric acid solution, as well as by hypertonic sea-water, cyanide, or high temperature (32°).

The optimum duration of exposure (with which 90 per cent or more eggs form larvæ) varies inversely with the concentration of butyric acid. The following table gives the optimum exposures for solutions of butyric acid in van't Hoff's solution (found in a series of experiments in the second week of June).

The approximate constancy of the product of concentration and time of exposure indicates that the butyric acid activates the egg by combining chemically with some egg-constituent. The time required for the production of a definite quantity of reaction-product (the critical

CONCENTRATION OF BUTYRIC ACID (C)	OPTIMUM TIME OF EXPOSURE (T)	PRODUCT (C × T × 1000)
0.00075 n.	*ca.* 42 m.	31.5
0.001 n.	*ca.* 35 m.	35
0.0015 n.	20–25 m.	30–37.5 (av. 34)
0.002 n.	*ca.* 15 m.	30
0.0025 n.	12–14 m.	30–35 (av. 32.5)
0.003 n.	8–12 m.	24–36 (av. 30)
0.004 n.	6– 7 m.	24–28 (av. 26)

quantity required for complete activation) should, according to the mass-action law, be inversely proportional to the concentration of the butyric acid (since the concentration of the egg-constituent is to be regarded as constant). The nature of the compound formed is problematical. A typical base like ammonia has no effect in activating the starfish egg. A chemical combination in which an acid takes part is thus indicated as the first stage in the activation of this egg.

The permeability of animal and plant cells. W. J. V. OSTERHOUT.

On the rôle played by electrolytes in determining the permeability of protoplasm. G. H. A. CLOWES.

Three types of muscular response in sea-anemones. G. H. PARKER.

The relation of certain muscles to oxygen. F. S. LEE, A. E. GUENTHER and H. E. MELENEY (by invitation).

Influences affecting voluntary muscular work—especially age and tobacco. WARREN P. LOMBARD.

The following is a contribution to individual physiology. The subject has always had excellent health, and has led the regular life of a teacher. In December and the following spring of 1890, when thirty-five years old, he made a careful study of the influences which affected his endurance for voluntary muscular work. In the late summer of 1915, when he was sixty years old, he repeated the experiments, using a duplicate of the old apparatus, and the same methods of work. The flexor muscles of the second finger raised a weight every two seconds, always as high as possible, and this was continued until the greatest possible effort failed to raise the weight. The work was repeated at two hour intervals eight times a day, and during a few days throughout the twenty-four hours. The height to which the weight was lifted by the separate contractions was recorded, and the total amount that the weight was lifted was read off from a work adder.

The experiments showed that his endurance in 1915 was affected by the same influences as in 1890; it was increased by the rest of a night, a meal, and rising atmospheric pressure; and decreased by general fatigue, hunger, falling atmospheric pressure, and smoking; moreover, his diurnal curve of endurance was the same, it being greater at nine to ten o'clock in the morning and nine to ten o'clock at night, and less at

four to five o'clock in the afternoon and four to five o'clock in the morning. In spite of the fact that he was twenty-five years older, and had done no special work with the muscles in question, his capacity to increase his endurance by training was greater in 1915 than in 1890. In his case, the central nervous mechanisms engaged in the work appear to give out before the peripheral nervous mechanism and the muscles, and it is probable that it is the central nervous system which is chiefly affected by the influences which determine the amount of work that he can do at a given time. If this be true, the greater capacity to increase his endurance in 1915 as compared with 1890, may be the result of the continuous training to which his nervous system has been subjected during the past twenty-five years.

For a number of years preceding 1890 he had the habit of smoking four to five cigars a day, and the number had increased to six or seven a day in 1915. Smoking was found to decrease the endurance in 1915 as in 1890; this effect did not prevent an increase of endurance as a result of training, even when six or seven large cigars were smoked daily; the increase was not as rapid, however, as when no cigars were smoked. Both the dropping of smoking and the resuming of the habit resulted in a temporary lessening of the endurance.

The function of the kidney when deprived of its nerves. WM. C. QUINBY.

Electrocardiographic studies in normal infants. EDWARD B. KRUMBHAAR.

To determine the normal electrocardiogram at different periods of infancy and childhood, records have been taken on 42 subjects from the ninth month of fetal life to twelve years of age. It was found that the fetal heart causes a simple upright monophasic curve. Records made before and after cutting the umbilical cord suggest that the functional capacity of the infant's heart is depressed by this procedure. At birth a right ventricular preponderance is present; the different features of which disappear with considerable constancy by the second or third month. By the sixth month, the infant's electrocardiogram is practically the same as the adult's, except that Q_2 and Q_3 are apt to remain unduly prominent beyond this period. The P–R interval is shorter and sinus arrhythmia is practically absent in the first year. Sinus arrhythmia increases in frequency from the sixth to the twelfth year.

The time relations of auricular systole. CARL J. WIGGERS.

Simultaneous tracings of auricular myograms and intra-auricular pressure curves, were recorded by optical systems. The records presented led to the following conclusions:

1. A short interval after excitation each unit of cardiac tissue begins to contract and continues in this condition on an average, for 0.047 second.

2. When the approximation of two points on the auricle is recorded accurately, the myogram shows three phases: (a) when the contraction of each cardiac unit progresses from one lever attachment to the other, (b) when all auricular tissue is contracting and (c) when contraction of

one portion goes on at the same time with relaxation of another. This total interval lasting on an average 0.077 second may be designated the *mechanical contraction*.

3. As the rise of intra-auricular pressure precedes *mechanical contraction* of the auricle, on an average, by 0.019 second this interval should be added to the period of the mechanical contraction in order to estimate the entire *systole* of the auricle, which equals on an average 0.11 second.

4. The auricle increases tension within its cavity and that of the ventricle *only* during the early half of its systolic period. The *dynamic systole*, as this portion of the curve is termed, averages 0.0533 second.

5. The interval between the end of auricular systole and beginning of ventricular systole averages 0.0165 second making the A_s V_s interval 0.132 second.

The movements of the mitral valves in relation to auricular and ventricular systoles. A. L. DEAN (by invitation).

Further researches on the relation of the chromotropic action of the vagus to the nodal tissues. H. STEENBOCK, J. A. E. EYSTER and WALTER J. MEEK.

The tension of carbon dioxide and oxygen in the venous blood at rest and at work. WALTER M. BOOTHBY and IRENE SANDIFORD.

If the circulation rate and the arterial (alveolar) carbon dioxide and oxygen tensions are known it is possible, as is shown in our previous paper,[1] to calculate the tension of carbon dioxide and percentage saturation of the haemoglobin in the venous blood.

The carbon dioxide tension can be calculated as in curve VIII, figure IV, making allowance for the effect of partial desaturation of the haemoglobin on the dissociation curve of carbon dioxide or it may be plotted without this correction as though the haemoglobin remained saturated.[1]

This uncorrected venous carbon dioxide tension calculated from the same data as the other curves in figure IV is as follows:

OXYGEN CONSUMPTION	UNCORRECTED VENOUS CO_2 TENSION
cc.	*mm.*
175	47.8
200	48.5
300	51.9
400	54.5
500	56.5
600	58.7
700	60.3
800	61.3
1000	64.0

[1] Boothby: A determination of the circulation rate in man at rest and at work 1915, Amer. Jour. Physiol., xxxvii, 2.

Since the publication of the above paper we have performed two hundred and forty-four experiments on the direct determination of the uncorrected venous carbon dioxide and oxygen tensions according to the recent method described by Christiansen, Douglas, and Haldane.[1]

We have averaged these new experiments in the same manner as those in the previous paper and the results are given in the following table:

OXYGEN CONSUMPTION	UNCORRECTED VENOUS CO_2 TENSION
cc.	*mm.*
225	51.5
473	57.0
600	60.0
708	62.4
805	63.3

The points as determined fall on a line parallel to but from 1 to 2 mm. higher than the curve calculated from the data of the previous experiments.

This discrepancy, while slight, is consistent with the constant errors existing in the two methods of experimentation. In both methods the assumption is made that none of the blood makes a complete circuit during the time of the experiment; in the first set the error from this assumption will cause the calculated tension to be slightly too low; in the present series the same constant error will cause the tension determined experimentally to be correspondingly too high.

The points for the percentage saturation of the haemoglobin are fewer in number and do not correspond to the calculated curve as well as in the case of the carbon dioxide tension. The technic is more difficult with oxygen, especially at work, and the inhalation of pure nitrogen makes the experiments somewhat dangerous so that their number was limited.

The following table gives the percentage saturation of the haemoglobin determined experimentally for various oxygen consumptions:

OXYGEN CONSUMPTION	PERCENTAGE SATURATION HAEMOGLOBIN
cc.	*mm.*
225	69.5
603	59.0
704	53.1

The chief physical mechanisms concerned in clinical methods of measuring blood-pressure.[2] CLYDE BROOKS and A. B. LUCKHARDT.

[1] Christiansen, Douglas, and Haldane: The absorption and dissociation of carbon dioxide by human blood. 1914, Jour. Physiol., xlviii, 4.

[2] Paper published in full elsewhere in this number.

Haemodynamical studies. R. Burton-Opitz. Read by title.

The mechanism of the arterial compression sounds of Korotkoff. Joseph Erlanger.

The responses of the vasomotor mechanism to different rates of stimulation. Charles M. Gruber.

The response of the vasomotor mechanism is affected by different rates as well as by different strengths of stimuli. A long series of experiments upon cats under urethane anaesthesia showed that slow rates 4 to 6 per second are favorable in bringing about a reflex fall in blood pressure and a rapid rate 20 per second is favorable in bringing about a rise in blood pressure, when the current is weak (5.8 to 17Z units). When the current is strong, 494Z units, a slower rate 1 per two seconds or 1 per second interruption is favorable in producing reflex vasodilation.

Vasomotor summations. E. G. Martin and P. G. Stiles.

Blood changes following hemorrhage and perfusion. Theodore Hough and J. A. Waddell.

Five dogs and three rabbits bled from artery or vein and immediately perfused with 0.9 per cent saline or with 0.9 per cent saline and 2.5 per cent gelatin. Counts of reds and whites, and hemoglobin determinations; in one animal daily duplicate determinations of each of these for a period of eight weeks. (1) The post-hemorrhagic fall of hemoglobin and reds, noted by previous observers, occurred generally with saline perfusions, but was absent in four out of the five cases of gelatin-saline perfusion. (2) When regeneration began to show its effect two to four days after hemorrhage, in all animals but one the color index (ratio of hemoglobin to erythrocytes) rose and for at least two or three weeks remained above normal. This indicates that the newly formed corpuscle contains more hemoglobin than those that have been longer in the circulation; that is to say, erythrocytes may and generally do undergo a gradual loss of hemoglobin. (3) The discharge of new erythrocytes on the blood is not a steady process but shows a distinct tendency, in the rabbit at least, to be intermittent. Periods of increase for one or more days were followed by a constant count or even by a fall for several days; then would come another rise. (4) Each rise in the erythrocyte count is accompanied by a distinct rise in the leucocyte count either on the same or the preceding day. It is believed that, in general, when other causes of leucocytosis are controlled or absent, the leucocyte count may be taken as an indication of the degree of activity of the blood forming organs. (5) Periods, lasting from two to six days, of apparent instability of the erythrocytes were observed from time to time. This showed itself in the number of ghosts or the tendency of the erythrocytes to fragment and go to pieces after being mounted on the counting slide. There were indications

that the older rather than the newly formed corpuscles were affected by this hemolytic action. (6) The tendency of the color index to rise during the first period of regeneration may give place later to a fall which results in its remaining below normal for weeks, despite frequent periods of hematopoiesis. It is suggestsd that the manufacture of hemoglobin calls for an unusual supply of certain amino-acids or other material which, during the early period of blood regeneration, can be furnished by the organism from the reserve supply of its own tissues; later, when this reserve is exhausted, only a limited amount of hemoglobin may be manufactured from the usual food and we may have, and generally at such times do have, a rise of the red blood count unaccompanied by any corresponding rise of the hemoglobin. In such cases hematopoiesis results in a lower color index, in contrast to what is observed during the first periods of hematopoiesis after the hemorrhage.

Experimental and clinical studies on mental defectives. III. The relation of systolic and diastolic blood pressures and their power of adjustment to body position. AMOS W. PETERS and CAROLINE D. BLACKBURN.

Feeble-minded inmates of an institution and some normal subjects were tested for the efficiency of the splanchnic vasomotor mechanism. The pulse rate and the systolic and diastolic blood-pressures were measured after stability had been established in first lying and then standing positions. It was desired to obtain a quantitative expression for the vasomotor tone of these subjects in terms of Crampton's scale of percentage condition. The expected age differences between children and adults in pulse rate and in systolic and diastolic pressures were observed. After changed posture the average pulse rate was increased by 11. The average systolic pressure increased only 4 mm. but the average diastolic pressure increased 18 mm., or in percentage of standing to lying as 2.4, systolic, to 32.1, diastolic. On Crampton's percentage scale of vasomotor tone the average of all the subjects showed a low result viz., 75 per cent. Their cardio-vascular adaptation is poor corresponding to their defective growth-development. Known irregularities in the auscultation phenomena in children (Katzenberger), vitiate the supposed differentiation by this criterion between the normal and the feeble-minded.

Prolonged uniform intravenous injections (Lantern). R. T. WOODYATT.

The destruction of hormones, pro-enzymes, and enzymes, by ultra-violet radiation. W. E. BURGE.

The hormones used were adrenalin and secretin; the pro-enzymes and enzymes, trypsinogen, trypsin, pepsin, ptyalin, amylopsin, taka diastase and enterokinase. Five cc. of a clear solution of the substance to be exposed were introduced into a circular glass vessel 5 cm. in diameter and 1 cm. deep. This was covered with a quartz plate 2

mm. thick to prevent evaporation and the vessel was partially immersed in running water beneath a quartz mercury-vapor burner operating at 140 volts, 2.3 amperes and 2400 cp. at a distance of 5 cm. The temperature of none of the solutions rose higher than 30°C. during the exposures.

The exposures were made for different lengths of time and the rate of destruction was found to be directly proportional to the length of exposure. All the substances were found to be destroyed after an exposure of about an hour.

When the vessel containing the substances exposed was covered with a clear piece of plate glass 5 mm. thick instead of the quartz plate none of the substances were affected after many hours' exposure. It had been determined that the glass cover used did not transmit wave lengths shorter than 313 $\mu\mu$ hence these shorter wave lengths were the ones which caused the destruction of the substances exposed. It had also been determined that only wave lengths 302 $\mu\mu$ and 297 $\mu\mu$ in the spectrum of the quartz mercury-vapor burner used were effective in coagulating protein. The assumption might be made that these are the specific wave lengths which cause the destruction of the enzymes, pro-enzymes and hormones.

Initial length, initial tension and tone of auricular muscle in relation to myo- and cardiodynamics. Robert Gesell.

Is the contraction of smooth muscle accompanied by heat production? (Second Communication.) C. D. Snyder.

A suitable smooth-muscle-nerve preparation has been made out of a ring of turtle's stomach with left vagus attached. The ring of muscle is slipped in place over a thermopile of the "Gittersäule" type and suspended in a specially devised moist-chamber.

When the muscle was made to contract by stimulating the nerve the results were of a contradictory nature. At times no heat exchange accompanied or resulted from the contraction; at other times equal tensions apparently were accompanied now by heat absorption now by heat production.

The same preparation, without being subjected to any manipulation, upon direct stimulation gave off heat in a wave of two maxima, as Bernstein has recently reported (Pflüger's Archiv, vol. 159).

The first wave of this heat production is doubtless due to the warming caused by the degraded electricity. The second maximum Bernstein further explains is due to the energy exchanges directly concerned with the muscle contraction. In the present author's experience this becomes doubtful for the reason that the same muscle, when dead and similarly stimulated with the electric current, again gave off heat in a wave of two maxima.

Lifting and the Valsalva experiment: effect on systolic pressure, heart rate and radial pulse curve in man. With a note on labor pains in a rabbit. Percy M. Dawson and Paul C. Hodges, University of Wisconsin.

The object of this research was to determine some of the immediate effects upon the circulation of "exercises of strain." By the latter are meant those muscular efforts which are performed with the glottis closed and which tend to compress the chest thereby causing a rise in intra-thoracic pressure. The forms of strain studied were the Valsalva experiment and lifting.

The Valsalva experiment consists in forced expiration with the closed glottis. The history of this maneuver is dramatic. It includes the account of the bandit, who committed suicide in the very presence of the unsuspecting Roman consul and thus eluded a cross-examination (Valerius Maximus); of Colonel Townsend, "the man who could die and come to life again" (Cheyne); and of the self-induced syncope of E. F. Weber.

The changes in systolic pressure were determined by the auscultatory method supplemented with the Erlanger sphygmomanometer, the inflation of the cuff being rapidly performed by means of highly compressed air. They consisted in (1) a rise first described by Riegel and Frank, '76, first measured by McCurdy, '02, (180–200 mm. Hg); (2) a fall first observed by Weber, '50. The extent of this fall is such that when the pressure in the cuff of the "Erlanger" is 60 mm. or more., no pulsation of the lever could be obtained by us; (3) a rise first observed by Bruck, '07. The latter states that this may reach 200 mm. but we were unable to obtain a rise above 140 mm. which is no more than that obtained by simply holding the breath for a similar length of time. Following the effort the pressure remains elevated subsiding with the disappearance of dyspnea.

The changes in heart-rate were determined with the string galvanometer. They consisted in (1) a slowing (often absent) occurring as soon as the effort began; (2) a quickening first observed (but not measured) by Riegel and Frank, which reaches its maximum shortly after the cessation of the effort; (3) a great slowing followed by a more or less gradual return to normal. For example normal length of cardiac cycle was 0.68 second, at (1) 0.94 second, (2) 0.46 second, (3) 1.26 second, returning again toward normal 0.88 second. These variations are confined to diastole. The A–V interval is unaffected.

The pulse wave was studied with the Dudgeon sphygmograph (weighed after Lewis, '96). The results obtained confirmed those of Riegel and Frank, whose findings have been adequately explained by themselves and by Hill, Bernard and Sequeira, '97.

In a second series of experiments (not yet quite completed) lifting was substituted for the Valsalva experiment. Up to the present our results are similar.

By chance we obtained mean blood pressure and respiratory records in a rabbit during labor. The latter was induced by stimulation of the

sciatic under urethane and chloral anesthesia. Accompanying the labor pain there was a rise in pressure and slight slowing of the heart rate (accompanied by cessation of the respiratory movements), followed by a fall in pressure to below normal. The return (rise) to normal occupied about 30 seconds.

Comparative studies in the physiology of the gastric hunger contractions in the amphibia and the reptilia. T. L. PATTERSON.

The comparative studies on the amphibia and the reptilia were made on the bullfrog (Rana catesbiana), and the common snapping turtle (Chelydra serpentina), respectively. The usual operative method of procedure was modified in the case of the bullfrog while the ordinary gastrostomy was performed on the turtles. All the bullfrogs were stomostomized. This simple operation consisted of making a circular opening on one side between the ramus of the inferior maxillary, near the angle, and the anterior cornua of the hyoid bone through the skin, the mylohyoid muscle and the lining membrane of the mouth of sufficient size to admit the balloon and the attached rubber tube which connected with the recording manometer.

The gastric tonus in both the frog and the turtle remained practically constant throughout the experimentation. In the turtle, however, there was a marked increase in the amplitudes of the hunger contractions during prolonged starvation directly proportional to the length of the fast and the same was indicated in the frog. The author[1] in a previous paper has shown in the dog that there is a marked increase in the gastric tonus in prolonged starvation, and that this increase is inversely proportional to the decrease in the amplitudes of the hunger contractions. This is just the reverse of what is found in the case of the frog and the turtle. The gastric hunger contractions in the frog were continuous but the hunger movements of the turtle showed periodicity which is one of the characteristic factors used in differentiating the gastric hunger movements from digestive peristalses in all the higher animals so far experimented upon.

From X-ray studies made on the frog's stomach by means of the bismuth coated balloon, as well as observations made on the excised stomach of the same animal the gastric contractions were found to be peristaltic, the peristaltic waves originating within about 1 cm. of the cardia and advancing rhythmically over the stomach. When water, Na_2CO_3—1 per cent solution and HCl—0.5 per cent solution were introduced directly into the stomach of the frog without coming in contact with the mouth they invariably produced inhibition varying in degree with the stimulating power of the substance introduced, it being most marked in the case of the acid and least in the case of the water. When these same substances were introduced directly into the mouth cavity the inhibitory effects produced were very slight, thus indicating that the cerebral processes were not as highly developed as in the case of the higher animals, since introduction of these substances into the mouths

[1] Patterson: Am. Jour. of Physiol., 1915, xxxvii, 316.

of higher animals is followed by a marked inhibition. The gastric hunger movements are not affected by the removal of the cerebral hemispheres, the graphic record of the normal and the decerebrate animal remaining practically the same which shows again that the cerebral processes exerts no appreciable influence on the gastro-neuro-muscular apparatus of the frog. Records of the frog shortly after feeding showed but very little change from the stomach of the hungry animal, the only observable variation being perhaps a very slight increase in the rate of the contractions. The introduction of the previous mentioned substances directly into the stomachs of higher animals normally produces gastric hunger inhibition but has scarcely no effect upon digestive peristalis, however, in both the hungry and the filled stomach of the frog similar inhibitory effects were produced by them. Therefore, we are justified it seems to me in drawing the conclusion, that in the frog at least, we have a much simplified gastric mechanism which through the processes of evolution has evolved itself in the higher animals into the gastric digestive peristalses and the gastric hunger contractions, the latter of which perhaps may be described as intensified gastric digestive peristalses.

Localization by faradic stimulation in the floor of the fourth ventricle. F. R. Miller.

By employing the method of unipolar faradization it is possible to determine the location of a number of functions in the floor of the fourth ventricle.

Sherrington and Miller localized deglutition at the inferior fovea. Since the fasciculus solitarius approaches the surface at this point it appears probable that the swallowing is evoked by the stimulation of afferent fibres of the glossopharyngeal and superior laryngeal nerves contained in the fasciculus. By stimulating the same point a secretion of saliva is elicited from the ipsilateral parotid and submaxillary glands, the flow from the parotid being the greater. These glandular effects are probably produced reflexly by stimulation of afferents in the fasciculus solitarius. Salivary secretion may also be excited at two points near the middle line of the medulla at the level of the striae medullares; the anterior point yields submaxillary the posterior point parotid secretion. These two effects probably depend on the stimulation of efferent fibres to the respective glands. With the aid of unipolar stimulation the centres for cardiac inhibition and for movements of the stomach and small intestine were localized in the dorsal vagus nucleus (ala cinerea). These latter results are in agreement with those which Van Gehuchten and Molhant arrived at by histological methods.

Direct evidence of duodenal regurgitation and its influence upon the chemistry and function of the normal human stomach. William H. Spencer, George P. Meyer, Martin E. Rehfuss, and Philip B. Hawk.

The absence of bile in the stomach when certain materials are introduced and its presence with certain other substances renders bile an

uncertain indicator of regurgitation of duodenal contents. The varied results of investigators on this subject can be attributed to their use of bile for this purpose. The uncertainty of the presence of bile led to our further investigating the theory of Boldyreff as to the self-regulation of the acidity of the contents of the stomach by regurgitation of alkaline duodenal juices.

The quantitative estimation of trypsin by the method of casein digestion, was done upon the samples obtained by fractional analysis of the gastric content. Various materials were introduced into the fasting stomach (previously emptied of residua) of normal healthy men and the trypsin values compared with the reaction of the gastric content at ten minute intervals.

Trypsin proved to be the ideal indicator of duodenal regurgitation and was found to be almost constantly present in the fasting and digesting content of the normal human stomach.

In general, the tryptic values were high in gastric contents of low acidity and of alkaline reaction, and low when the gastric contents were of high acid concentration. A fall in acidity was usually accompanied by a rise in tryptic values. When bile was present the tryptic values of the gastric content usually rose, concomitantly with the color changes, but in a non-bile stimulating diet trypsin was constantly present where no traces of bile were found.

0.5 per cent HCl ingestion was followed by a rapid fall in acidity to about 0.2 per cent HCl acid due to a regurgitation of alkaline duodenal contents, as is indicated by a rise in tryptic values coincident with the fall of the acidity.

Sodium bicarbonate in 0.5 per cent solution is held in the stomach until sufficient HCl is secreted to bring the alkalinity to a point where it is non-irritating to the duodenum. The retention is accompanied by high trypsin values—suggesting regurgitation in response to duodenal irritation. Sodium bicarbonate in 0.1 per cent solution hastens the emptying of the stomach either by increasing the motility of the stomach or opening the pylorus.

Sodium bicarbonate solutions do not inhibit human gastric secretion, but seem to have a direct stimulatory effect in most cases. Free HCl appears unnecessary for the opening of the pylorus, for the stomach sometimes empties while its contents are still alkaline in reaction.

Our work in many ways confirms the theory of Boldyreff. This phenomenon of regurgitation occurs however, not only with high acidity but when the gastric contents are made alkaline in reaction and seems to be a constant accompaniment of normal gastric digestion.

The diuretic action of tissue extracts. FRANK P. KNOWLTON.

The appearance of sugar in the digestive secretions of phlorhizen glycosuria. ROY G. PEARCE.

It is generally held that phlorhizin produces a glycosuria by exerting a specific action on the renal mechanism. In the present research the

salivary, gastric and pancreatic juices of normal and phlorhizinized animals have been examined with regard to their reducing power. While in normal dogs, whose blood sugar was less than 0.13 per cent no sugar could be demonstrated in the above juices, in the case of phlorhizinized dogs a reducing substance was found practically without exception, in the pancreatic and gastric juice, and often in the saliva. The kidneys are not necessary for the production of the phlorhizin effect, inasmuch as ligation of the renal vessels previous to the administration of phlorhizin does not alter the result. The percentile amount of reducing substance present in the juices was in all cases less than that present in the blood at the time of the collection of the juice.

The results in connection with the discovery of Levene, which has been confirmed by Woodyatt, that the bile of phlorhizinized animals contains dextrose, suggest that phlorhizin does not exert a specific action on the renal cells in the production of phlorhizin glycosuria.

The rapidity with which alcohol and some sugars are available as nutriment. H. L. HIGGINS.

Some results of studies on electrical changes in glands. W. B. CANNON and MCKEEN CATTELL.

We have confirmed the observations of Bayliss and Bradford that an electrical change accompanies secretion by the submaxillary gland though the blood supply is cut off or the flow through the duct is stopped, and that the change is absent when secretion fails, though the conditions of secretion remain—changes in blood vessels and blood flow. We conclude therefore that the electrical change is a manifestation of the secretory process.

The direction of the action current from the submaxillary gland may be reversed although secretion occurs as usual in response to stimulation. Reversal is therefore not a sign of a reversed process in the gland.

Stimulation of the sympathetic cord in the thorax or in the neck causes an action current in the thyroid gland. Its latent period (5 to 7 seconds) is much longer than that of the submaxillary. It occurs after the laryngeal nerves are severed. It does not follow injections of pituitrin or pilocarpine, but is marked after injections of adrenalin. It appears on stimulating the adrenal gland through the splanchnic nerves. It is only slight and temporary after anemia mechanically produced.

The latent period of the action current of the adrenal glands is about fifteen seconds. We have recorded the action current of the pancreas after secretin injections, and a plan for a comprehensive study of the glands of internal secretion is now being carried out.

The action of the depressor nerve on the pupil. JOHN AUER.

Stimulation of the depressor nerve in white rabbits narcotized by the subcutaneous injection of 5–10 mgm. of morphine sulphate per kilo, usually causes a definite diminution in size of the pupil. This

contraction in typical cases is composed of two stages: a sharp prompt, short initial contraction followed by a slower, gradual contraction. Often only the initial contraction is observed, at other times only the slower, gradual contraction.

The initial contraction, when present, is obtained as soon as the nerve is stimulated, before the blood pressure begins to fall. The slower contraction occurs while the blood pressure is falling, and the iris blanches at the same time.

Stronger stimuli are necessary to cause this contraction of the pupil than suffice to bring on the characteristic drop of blood pressure. A strong fall of blood pressure due to a moderate depressor stimulation does not cause any alteration of the pupil.

Stimulation of one depressor may cause a contraction of the pupil on the opposite side.

This pupillary effect cannot be obtained with the same certainty as the fall in blood pressure. After several successful trials, the pupil usually fails to respond for a while.

The two depressors vary in their pupillary effect; one may yield excellent pupillary contractions, the other one none at all.

The stimuli used were rarely longer than five seconds; the strength 100–150 mm. coil distance (Petzold coil).

Section of the sympathetic nerve, or extirpation of the superior cervical ganglion, the depressor of the same side being stimulated several days later, exerts no appreciable effect on the result. The reflex therefore seems to act on the third nerve chiefly, if not entirely.

In addition to this pupillary effect, depressor stimulation at times causes a short wink or a more or less prolonged retraction of the bulbus.

It must be added that a strong winking (closure of the lids being prevented by a speculum) usually causes a very short sharp contraction of the pupil, the Piltz-Westphal phenomenon. This contraction is, however, more rapid than what has been described as the initial contraction on depressor stimulation; moreover, the initial contraction is frequently obtained without any sign of winking.

In rabbits anaesthetized by ether, or which have been allowed to recover from the ether, the depressor pupil effect was not obtained. An increase of reflex irritability is apparently necessary in order to obtain pupillary contraction on depressor stimulation.

Evidence showing the metaphore to be a disguised type of smooth muscle. Raymond Spaeth (by invitation). Read by title.

The voluntary innervation of skeletal muscle. E. G. Martin and R. W. Lovett (by invitation).

Comparison of the chemical changes in the central nervous system in pellagra and in animals on an exclusive vegetable diet. M. L. Koch (by invitation) and Carl Voegtlin.

A study of a lecithin-glucose preparation. Ernest L. Scott.

Lecithin was emulsified by shaking with water in the usual manner and, after having been well mixed with a sugar solution was evaporated to dryness on a water bath. In this way the alcohol was eliminated from the process though we still have a temperature which it is impossible to consider as occurring in an organism. However, in every case a "compound" was obtained which gave all the characteristic reactions of Bing's preparation, i.e., it was precipitated from an ether solution by the addition of a small amount of alcohol. A substance is obtained which is soluble in ether and benzene and from such solutions glucose may be obtained. This glucose precipitates to some extent from a clear solution which has been allowed to stand for a few days but is apparently quantitatively removed by repeated drying and solution in ether. An emulsion of a neutral fat (peanut oil) in place of lecithin treated in a similar manner failed to give any trace of any of the above reactions. One preparation has been prepared giving all of the above reactions which was dried by vacuum desiccation at room temperature.

The rotation of light by an ether solution of the preparation was compared with that of a similar solution of lecithin, and for the lecithin solution $[\alpha]^{D}_{20}$ was found to vary about 85 while that for the preparation varied about 135.

This preparation was further studied by comparing the freezing point of a benzene solution of it with that of a similar solution of the parent lecithin. The results, however, indicate a reaction between solute and solvent and so are inconclusive. It is hoped that further search will reveal a suitable solvent for use in the freezing or boiling point determination. Freezing point determination of lecithin emulsions containing small amounts of glucose indicate a loss of molecular concentration equivalent to 10 per cent to 60 per cent of the glucose present depending upon its concentration.

All of the added sugar may be recovered from such a preparation by removing the lipoid with colloidal iron and estimating the glucose by reduction. If it is supposed that such a compound exists in the blood this falls in line with our experience in estimating the blood sugar. A few qualitative experiments indicate that all of the sugar may be removed from such a preparation by dialysis.

The results so far obtained warrant us, we believe, in continuing the work and perhaps extending it to cover other physical-chemical properties and to other substances, as cholesterol, with which sugar of the blood and tissue might combine.

Effect of excluding pancreatic juice from the intestine on the absorption of nitrogen and fat. Joseph H. Pratt.

Metabolism experiments were conducted on six dogs in which the attempt had been made to exclude all the pancreatic secretion from the intestine. In four of the animals the operation was successful and all

of these showed a marked disturbance in the absorption of nitrogen and fat. Extreme atrophy of the pancreas developed. One animal was studied over a period of two and a half years. During this time eight metabolism tests were made. The disturbance in absorption persisted. The animal finally died of inanition.

The feeding of fresh pancreas and pancreatic preparations resulted in better assimilation of the food. On an exclusive milk diet the fat was well absorbed. In one of the two animals in which there was some escape of pancreatic juice into the intestine there was a moderate disturbance in absorption. In this case only a portion of the pancreas remained unatrophied. In the other dog the absorption was normal. Here the pancreas was unchanged and the communication between the pancreatic ducts and the duodenum had been re-established. When a bit of pancreas measuring 1 cm. in size was left attached to the open main duct there was only a slight disturbance in absorption. A test made nearly six months after the operation and three weeks before the death of the animal showed that 75 per cent of the nitrogen and 66 per cent of the fat were absorbed. At the autopsy on naked eye examination there was nothing that could be recognized as pancreatic tissue in contact with the duodenum.

None of the animals developed diabetes. The fat in the feces was well split. No abnormality was discovered in the gastric digestion.

The fat of the blood in relation to heat production, narcosis and muscular work. J. R. Murlin and J. A. Riche.

The major portion of these observations have been reported in a brief communication to the Society for Experimental Biology and Medicine (*Proceedings*, 1915, xiii, p. 7). To these we wish to add the observation that muscular work alters the percentage of blood fat. Dogs permitted to run in a tread mill for one hour at the rate of about four miles per hour, exhibit within the first half hour, sometimes within fifteen minutes, a fall in the percentage of blood fat. At the end of an hour, however, the percentage invariably rises (in carotid blood) above the normal. At the end of an hour's rest following the run the percentage has returned to or below the level which it had before the run. The fluctuations are greater in fat than in lean dogs.

The fat and lipase content in the blood in relation to fat feeding and to fasting. C. W. Greene and W. S. Summers.

The discovery of the reversible action of lipase by Castle and Loevenhart gave a key, therefore a new impetus to the investigation of the problems of fat transportation and fat metabolism in the animal body. Among the numerous recent papers on fats very little attention has been given to the synchronous variation of fat and lipase content. This relation we have examined in the blood chiefly of dogs under the conditions of prolonged fasting, and immediately following a fat meal.

The fats have been determined by the nephelometric method of

Bloor,[1] and the lipase by the method of Loevenhart,[2] using $\frac{N}{20}$ sodium hydrate titration of the butyric acid liberated by the lipase acting for a constant time and temperature.

After feeding. The blood of puppies quickly shows a variation in lipase and fat after a meal of milk and cream. The variation has been studied on sets of puppies of the same litter. When killed at three, five, eight, eleven and fourteen hours after feed the blood shows a curve of sharp increase in fat at the fifth to eighth hour, and a smaller increase to the eleventh or fourteenth hour in comparison with the normal. The blood lipase increases slightly during the interval of absorption. Adult individual dogs put on feed after a prolonged fast show only a slight increase in blood fats, but a very marked increase, double and more, of lipase lasting through two or three days before return to an average level.

During fasting. The blood of fasting puppies killed at successive fasting intervals shows a marked increase in the blood fats amounting in one series to 230 per cent of the normal on the eighth day, and 185 per cent on the ninth or last day of the fast. In the meantime the lipase of this series remains about constant for two days, rapidly falls to 45 per cent of the normal at four to six days, and sharply increases to 125 per cent on the ninth day. The cycle of changes occurs in a shorter time with younger animals. The apparent absolute amount of lipase increases with the age of the animals.

In adult dogs fasted for seventeen to twenty-two days intervals, the striking fact is the uniformity of content of fat in the blood. There is a tendency to lower fat content during twelve to fifteen days with a possible upward tendency after fifteen days, both within the limits of experimental error. The lipase curve is typical and like that of the fasting puppies, viz.,a decrease to half the normal or less in four to five days, a persistent low content to six to eight days, after which there is a very regular and even rise in lipase content to the end of the fast. The lipase level in every test on adult dogs was higher at the end of the fast than at the beginning, a fact that is significant in connection with the marked rise of both lipase and blood fats at the end of the series with the young animals.

Some practical applications of feeding experiments with albino rats. THOMAS B. OSBORNE and LAFAYETTE B. MENDEL.

The method of feeding which we have used with success in demonstrating the relative nutritive value of the different proteins for either growth or maintenance has been employed for determining the value of several of the concentrated feeding stuffs which are largely used as protein supplements in the rations fed to cattle and other domestic animals. These products have heretofore been valued solely on the basis of the *amount* of protein which they contain, no attention having been paid to the qualitative character of the protein.

[1] Bloor: Jour. Biol. Chemistry, 1914, xvii, 377.

[2] Loevenhart: Am. Jour. Physiology, 1902, v, 334.

In supplementing a diet of which corn or corn meal forms the chief constituent our experience indicated that better results would be obtained if the protein concentrate contained protein rich in tryptophane and lysine. The results of the experiments thus far conducted have shown this to be true, and plainly indicate that economies can be effected by using proper combinations of these relatively expensive food products. Comparisons already have been made by this method of such products as distillers' grains, brewers' grains, cotton-seed meal, fish meal, and beef meal. It is intended to continue these investigations and extend them to other largely used commercial products.

The influence of chemical substances on immune reactions with special reference to oxidation. AARON ARKIN.

Sodium iodoxybenzoate, an organic peroxide with physiologically active oxygen, has a marked germicidal action toward B. coli, typhosus, pyocyaneus and Staph. aureus, which differs for the different organisms.

Its action is most marked toward the organism containing the least catalase. These results suggest a relationship between catalase value of bacteria and their susceptibility to oxidizing agents.

The compound has a stimulating effect on phagocytosis in vitro. It stimulates the production of antibodies in immunized animals (hemolysin, agglutinin). It has an inhibitory effect on the local tuberculin reaction in tuberculous animals, and also reduces the toxicity of tuberculin in vitro. The substance does not influence the catalase value of the blood. A study of its effect on the catalase value of the tissues is now under way. These results, in the light of the pharmacological action of the substance, suggest that it stimulates the production of antibodies because of some catalytic effect by accelerating oxidations in the tissues which are the site of antibody formation.

The effect of thyro-parathyroidectomy on the blood coagulation time in the dog. SUTHERLAND SIMPSON and A. T. RASMUSSEN.

The object of this investigation was to determine whether removal of the thyroid gland (including parathyroids) in the dog had any effect on the blood coagulation time. The graphic method of Cannon and Mendenhall for measuring the coagulation time was adopted and found to work satisfactorily.

In all twenty-four animals were used. Two sets of observations under normal conditions were made, with an interval of a few days between, to find out whether the time varied appreciably from day to day. Then thyro-parathyroidectomy was performed and when the symptoms of parathyoid tetany appeared the coagulation time was observed again. The results show that no marked effect is produced on the coagulation time by the removal of these glands.

Detection with the string galvanometer of afferent impulses in the brain-stem and their abolition with ether anaesthesia. A. FORBES and R. H. MILLER.

The effect of ether anaesthesia must depend on the blocking of nerve impulses somewhere in the chain of neurones leading from sensory

receptor to motor end organ. Our experiments have sought to localize the action in some measure, and in particular to determine by means of action currents whether or not ordinary surgical anaesthesia blocks afferent impulses resulting from peripheral stimulation at the synapses through which they pass on their way to the cerebral cortex.

As a preliminary control it was necessary to ascertain whether in the nerve trunk profound etherization abolishes the action current which serves as an index of the nerve impulse. This point was investigated by one of us with McIntosh and Sefton. It was found that even under etherization pushed to the point of abolishing respiration action currents could be led off from a motor nerve under direct stimulation.

The peripheral afferent neurones extend centrally as far as the medulla oblongata. In view of the results with the nerve trunk we should expect no interruption of the action current by ether before this point. The effect of ether must be noted in some neurones central to the medulla. To obtain a suitable preparation that could be studied with and without anaesthesia decerebration was necessary.

Our experiments were made on decerebrate cats, observations being made at frequent intervals before, during and after anaesthesia by ether inhalation. Decerebration was performed under deep anaesthesia with the Sherrington decerebrator, and the best results were obtained with a transection at the anterior margin of the anterior corpora quadrigemina.

Action currents were recorded with the Cambridge String Galvanometer. For leading off electrodes we first used the porous "boots," later the gelatin type of Lucas, which are preferable. For stimulation single break shocks from a Berne inductorium were delivered through a pair of Sherrington shielded electrodes applied to the sciatic nerve.

When the leads were applied to the brain-stem the excursions of the galvanometer following the stimuli were small, but they were largest when one electrode was placed at the top of the brain-stem and the other at the bottom, and the direction of the major excursion indicates electrical negativity at the bottom. The procedure finally adopted was to place one electrode on the posterior corpus quadrigeminum on one side and the other at the base of the brain-stem 2 or 3 mm. the other side of the median plane. The stimulus was applied to the sciatic nerve on the same side as the upper electrode.

With this arrangement surgical anaesthesia with ether either greatly reduces the size of the excursions, or altogether abolishes them.

We are not prepared to draw generalizations concerning the degree of narcosis requisite for abolition of these nerve impulses, but we have found that abolition generally occurs long before respiration is interfered with. It is evident that if ether anaesthesia suffices to abolish or greatly reduce the magnitude of impulses in these neurones which arise in the medulla, it is more than likely that any impulse persisting in this region will be abolished in the next set of synapses in the chain leading to the cortex. It may then be fairly concluded that surgical anaesthesia protects the cerebral cortex from incoming nerve impulses.

A smooth-muscle nerve preparation. C. D. SNYDER.

Cinematograph and lantern demonstration of some effects on lesions of the nervous system. F. H. PIKE.

On the secretory discharge of the pituitary body produced by stimulation of the superior cervical ganglion. V. N. SHAMOFF (by invitation).

Concerning the action of various pituitary extracts on the isolated intestinal loop. V. N. SHAMOFF (by invitation).

The influence of certain cereal foods on the gastric secretion. C. C. FOWLER (by invitation), M. E. REHFUSS (by invitation), and P. B. HAWK.

Changes in the composition of the body of fasting lobsters. SERGIUS MORGULIS.

A note on the contractility of the musculature of the auriculo-ventricular valves. JOSEPH ERLANGER.

Kent[1] has recently described muscular tissue extending from the auricles onto the surface of the auriculo-ventricular valves. An examination of the literature as given by Nicolai[2] shows that muscle had been described in this locality by Reid in 1839, by Kürschner in 1840, by Paladino in 1876 and by Albrecht in 1903. In so far as we are aware, however, no one has recorded having observed contractions of these valve leaflets. The following observation seems therefore to warrant a brief note. It was made some years ago (June 3, 1911) while experimenting with the surviving beef's heart.[3] The heart had been perfused for some time. The ventricles had fibrillated; repeated perfusion with 1 per cent potassium chloride solution had failed to revive the rhythm of the heart; the auricles also had stopped beating. When the heart was opened, the posterior leaflet of the mitral valve was seen to be beating rhythmically. The movements were not very extensive. We were then of the opinion that under natural conditions contractions of such a strength would not play any very decided rôle in the normal action of the valves. The leaflet continued to beat after it had been cut entirely free of the heart. Histological examination revealed a few heart muscle fibers in the valve. This was the only instance in the course of a large number of experiments in which a valve leaflet was observed to be contractile. It would not be safe to draw any inferences as to the function of the musculature of the valve leaflets from an isolated observation that the valve musculature may be contractile, though feebly so, and spontaneously rhythmical, and at a time when the auricles themselves are not beating. Some of the pos-

[1] Proc. Roy. Soc., 1915, lxxxviii, p. 537.

[2] Nagel's Handbuch der Physiologie, 1905, i, 846.

[3] Erlanger: Am. Journ. Physiol., 1912, xxx, 395.

sibilities in the case are discussed by Nicolai (l. c.) and also by Kent (l. c.). Very recently Dean[4] has noted that before the end of auricular systole, the auriculo-ventricular valves very quickly ascend toward the auricle. Such a movement at this time might well be caused by a contraction of the valve musculature.

The psychic secretion of gastric juice. R. J. MILLER (by invitation), M. E. REHFUSS (by invitation) and P. B. HAWK.

[4] Proc. Soc. for Exp. Biol. and Med., 1915, xiii, 6.